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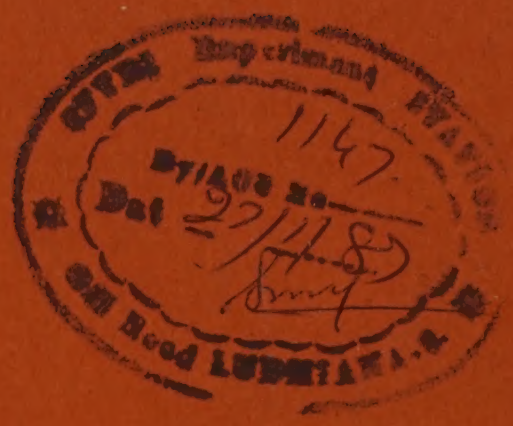

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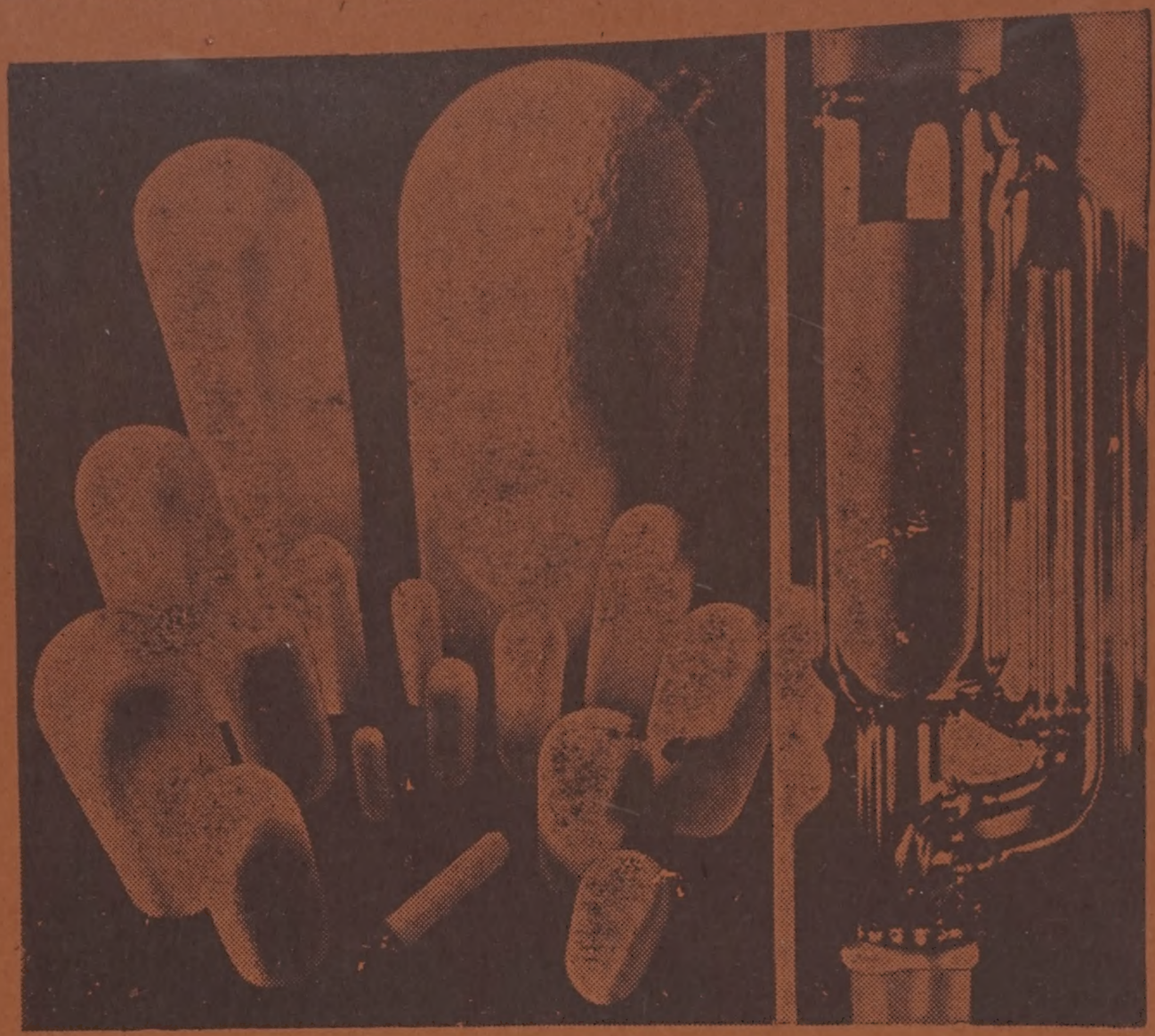

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Brassinosteroids

HARKISHAN SINGH* & TILAK RAJ BHARDWAJ
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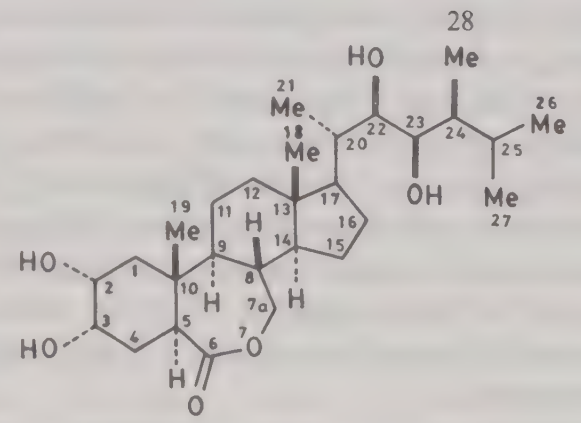
Steroids perform some of the most fundamental biological functions. They are of wide natural occurrence. Apart from the steroids of animal origin, the plant steroids are also of great significance[1]. There has been good interest in hetero modifications of steroids. Several heterosteroids occurring in plant kingdom are well known, and references to the literature have been cited[2]. A most recent finding is of heterosteroid brassinolide which is a plant growth promoting factor. This constitutes perhaps the most important discovery to the plant physiologists and biochemists since the discovery of gibberellic acid. The chemistry is also fascinating. Brassinolide and related products, collectively put as brassinosteroids, have evinced a great interest. In addition to naturally occurring products, several synthetic analogues have been prepared. Certain pattern of structure-activity relationship is also evident. The literature on different aspects of brassinosteroids is reviewed here.



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Brassinolide

Occurrence, isolation and structure

In early exploratory studies, an oily product isolated from rape pollen (*Brassica napus* Linn.) showed hormonal activity on assay by the bean second-internode test[3-5]. The product was a mixture and was termed as brassins. The spectral analysis indicated the brassins to be glucosyl esters of various fatty acids[6]. However, it was noted that 6-D-glucopyranosyl esters of palmitic, oleic, linoleic and linoleic acids identified in the rape pollen were inactive as plant growth promoters[7]. It was considered that pollen from plants other than rape may also contain hormones that are similar to brassins. For example, their occurrence in pollen from alder, *Alnus glutinosa* (Linn). Gaertn., was shown[3]. The validity of these early findings was questioned because biological activity was not correlated with any one pure compound[8].

In 1979, success was achieved in isolating a pure active component brassinolide from bee-collected *Brassica napus* Linn. (rape) pollen[9]. A partially refined 2-propanol extract of the pollen on chromatographic separation gave brassinolide (4 mg from 40 kg of pollen). The field desorption mass spectral fragmentation pattern indicated the structure **1**, confirmed by X-ray analysis of a single crystal.

Chemically, brassinolide is (22*R*,23*R*,24*S*)-2α,-3α,22,23,-tetrahydroxy-B-homo-7-oxa-5α-ergostan-6-one (**1**). The structure is novel in ways more than one. Seven-membered B-ring lactone system is unprecedented in natural products. Insect moulting hormone has 7-en-6-one grouping[1]. The side chain in **1** has four successive asymmetric centres. The rings A and B are *trans*-fused in contrast to *cis*-fusion in ecdysones. In ecdysones[1] 2,3-*cis* glycol system has mostly β orientation, but cases are known as of ponasterones B and C[10] which have α orientation of the glycol grouping as in brassinolide.

In addition to rape pollen, occurrence of brassinolide has been noted in immature seeds and sheaths of Chinese cabbage (*Brassica campestris* var. *perkinensis*) in extremely small amounts (<1 μg/320 kg)[11,12], leaves of green tea (*Thea sinensis*) (<1 μg/65 kg)[12,13], and insect galls of chestnut tree (*Castanea crenata*) (2 μg/3.5 kg)[14].

Plant growth-promoting activity

In the pinto bean second-internode bioassay, brassinolide (**1**) promotes both cell elongation and cell division, resulting in curvature, swelling and, more dramatically, splitting of the internode at doses as low as 10 ng per plant[9]. The growth rate of mung bean epicotyls has also been used for evaluating the effects of brassinolide on cell elongation[15].

Investigations have been carried out using a number of auxin[16], gibberellin and cytokinin[17] bioassays. Brassinolide exhibits an auxin synergism in the bean

hypocotyl hook opening, azuki bean epicotyl and dwarf pea epicotyl bioassays and also elicits strong growth-promoting effects in a certain other auxin bioassays. It is highly active in elongation bioassays employing the dwarf pea epicotyl and etiolated bean hypocotyl that are responsive to GA_3 but not indole-3-acetic acid (IAA) (at 0.01 to 10 μmol). The elongation of the cucumber hypocotyl elicited by brassinolide and GA_3 is reduced far more than that elicited by IAA, following removal of the cotyledons. While almost half as effective as kinetin in promoting expansion of cucumber cotyledons, brassinolide is ineffective in some other cytokinin bioassays. Unlike IAA, brassinolide does not interact synergistically with GA_3. The activity of brassinolide in promoting stem elongation in plant bioassays responsive to either IAA or GA_3, or to both, coupled with its effect on adventitious root formation, makes it a unique plant growth substance.

The other bioassay procedure of interest is the rice-lamina inclination test[18-20]. Brassinolide shows strong activity in stimulating the rice-lamina inclination at a very low concentration (0.0005 and 0.005 μg/ml), whereas IAA shows only a weak effect on lamina inclination at 50 μg/ml[19].

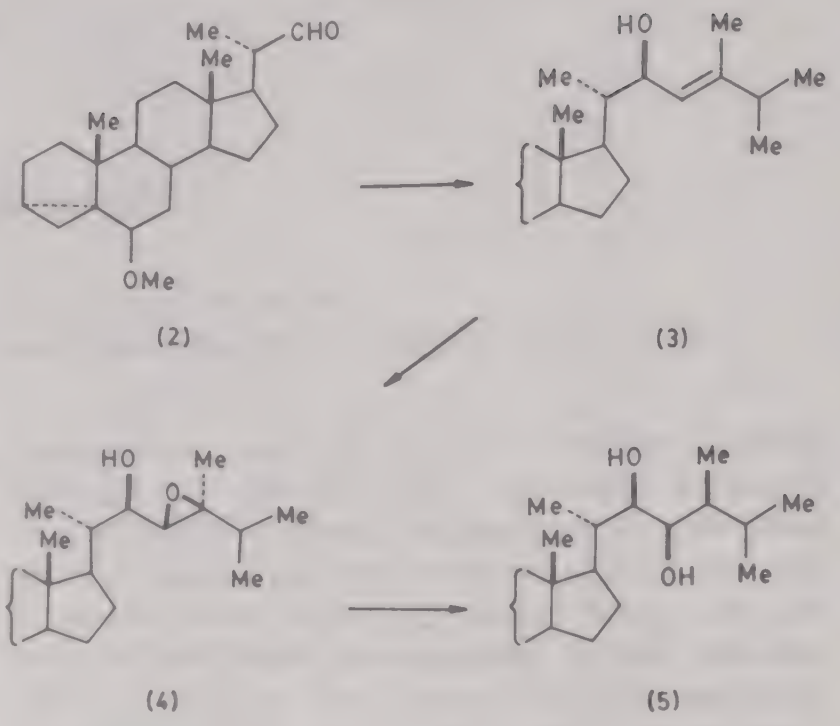
The bean internode and rice-lamina inclination tests employ plant segments to evaluate the biological activity of brassinosteroids. The activities of brassinosteroids in the promotion of growth of intact radish (*Raphanus sativus*) and tomato (*Lycopersicon esculentum*) plants have been reported[21]. Brassinolide supplied via the root system remarkably promots elongation of cotyledon petioles and hypocotyls of young radish and tomato plants at concentrations as low as 0.01 ppm, and also induces morphogenetic responses.

Applications of brassinolide analogues in agriculture have been examined in a preliminary form and the results have been promising[22].

Synthesis

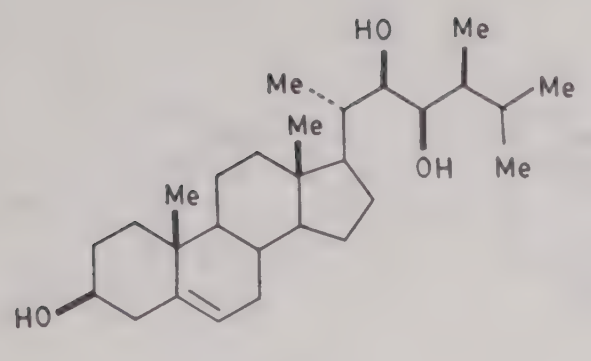
One of the interesting features in the preparation of brassinolide (**1**) has been the design of the side chain which has four consecutive chiral centres. The approaches to the construction of aliphatic side chains of steroids and related compounds have been reviewed[23,24]. In the synthesis of **1**, mostly the first choice has been to elaborate the side chain and then the nucleus. Two independent syntheses were reported in 1980[25,26].

In a stereoselective synthesis of **1**, Fung and Siddall[25] used 3,5-cyclo steroidal aldehyde **2**, prepared from stigmasterol. The chiral C-20 in **2** (same configuration as in stigmasterol) helped to generate asymmetry at C-22. Alkylation of **2** with lithium



butyldimethyl (*E*)-2,3-dimethylbutenylalanate gave predominantly the 22*S*-allylic alcohol **3**; the less polar 22*R*-isomer was only a minor product. Hydroxyl-directed epoxidation showed stereoselectivity and pure oxirane **4** was obtained. Anti-Markovnikov reduction of **4** with inversion at C-24 ($LiBH_4$, BF_3.THF; 50°C, 20 hr) showed 3:1 regioselectivity for formation of the glycol **5**. In another route, starting with **2** and making use of transition metal-catalysed silylmetalation of acetylenes approach, stereoselective synthesis of side chain has been achieved in the preparation of **5**[27]. The glycol **5** on acid-catalysed regeneration gave the 3β-hydroxy-5-ene **6**[25]. The latter, having configurations at C-20, C-22, C-23 and C-24 as in **1** has been prepared alternatively[28] through a route involving stereoselective reduction of appropriate steroidal 23-en-22-one with diisobutylaluminium hydride. Protection of the glycol grouping as the acetonide, tosylation, introduction of 6α-OH by hydroboration-oxidation, and elimination followed by Jones' oxidation gave the 6-ketone **7**[25]. The introduction of 2α,3α-diol system by stereospecific α-face hydroxylation (O_sO_4, C_5H_5N), deprotection, and Baeyer-Villiger oxidation (CF_3CO_3H in moist CH_2Cl_2/CF_3CO_2H) led to brassinolide (**1**) in good yield.

In the synthesis by Ikekawa and coworkers[26,29], the aldehyde **8** derived from dinorcholenic acid was reacted with 3-methyl-1-butynyllithium in tetrahydrofuran to give a 1:1 epimeric mixture of 22-alcohol, from which the more polar 22*R*-isomer **9** was isolated. Reduction with Lindlar catalyst afforded *cis*-allylic alcohol **10**, which stereospecifically gave epoxide **11** on oxidation with *t*-butyl hydroperoxide-oxovanadium acetylacetonate in benzene. The acetate derived from **11** was subjected to hydrocyanation followed by saponification, acetonide formation, and deprotection



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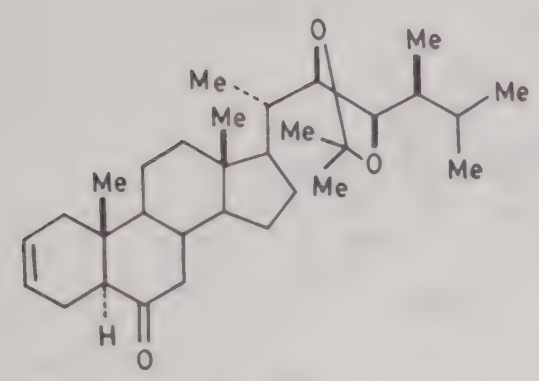

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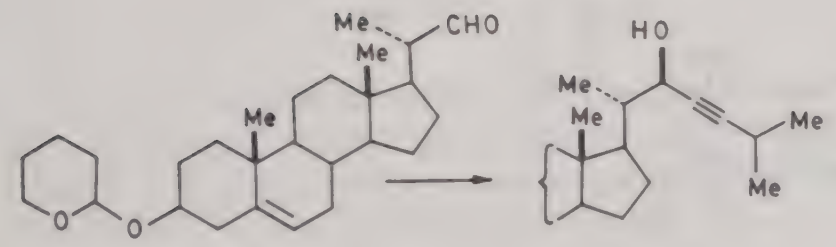

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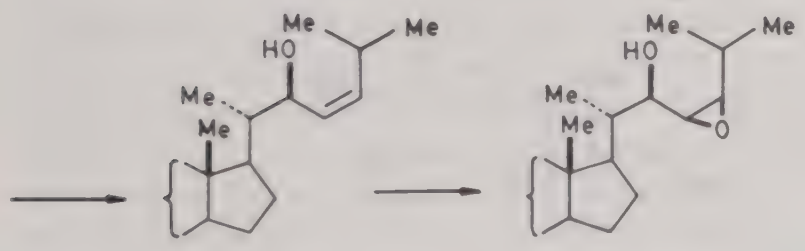

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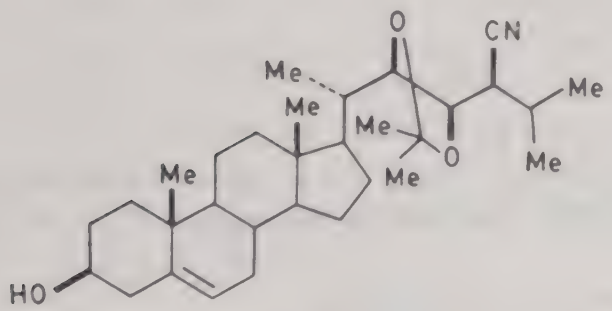


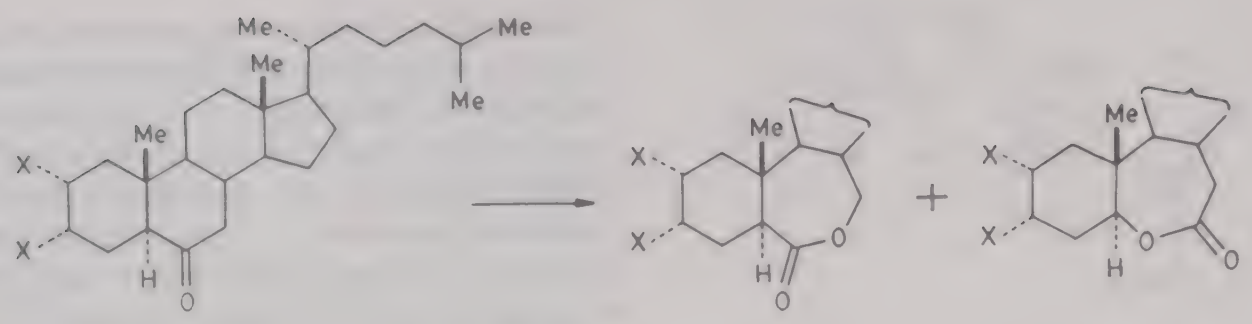
(12)

to give the nitrile **12**. From the nitrile function, methyl group was generated, and a series of steps led to **7**. The latter was used to obtain brassinolide (**1**), the ring-B lactone formation being carried out by Baeyer-Villiger oxidation with (22*R*, 23*R*, 24*S*)-2α,3α,22,23-tetra-acetoxy-5α-ergostan-6-one.

Before going further it is appropriate to take note of observations on Baeyer-Villiger oxidation of 6-keto steroids, since this reaction is a key one in forming the 7-oxa lactone moiety of brassinolide. In the Baeyer-Villiger oxidation, the migratory aptitude of alkyl groups with retention of their configurations decreases in the order tertiary, secondary, primary and methyl, as expected from their relative abilities to stabilise the electron-deficient transition state. It was reported that in the case of 5α-cholestan-6-one (**13**) this migratory aptitude held true; the *B*-homo-6-oxa-7-oxo lactone **15** was obtained as the major product upon the oxidation[30]. On the other hand, introduction of acetoxyl or halogen at 3β position affected the regioselectivity of the Baeyer-Villiger oxidation, and the *B*-homo-7-oxa-6-oxo lactones were also obtained[31,32]. In fact, in the presence of C-3 substituents migration of C-7 is more pronounced than in their absence. A further study of the Baeyer-Villiger oxidation of 5α-cholestan-6-one derivatives has shown that the regioselectivity is markedly affected by substituents at C-1, 2 and 3 positions[33]. For example, on treatment with 7 equivalents of trifluoroperacetic acid in dichloromethane in the presence of disodium hydrogen phosphate at 20°C, 2α,3α-dihydroxy-5α-cholestan-6-one (**16**) gave 7-oxa (**17**) and 6-oxa (**18**) lactones in ratio 92:8, whereas 5α-cholestan-6-one (**13**) yielded **14** and **15** in 30:70 proportion. The regioselectivity is evident in the work on the synthesis of brassinolide[25,29].

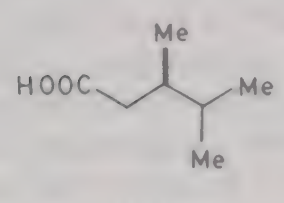
Coming back to the synthesis of brassinolide (**1**), it may be mentioned that in the syntheses cited earlier[25,26,29], the dihydroxy side-chain was constructed by first generating asymmetry at C-22 and then controlling the stereochemistry at C-23 by OH-directed epoxidation. Mori and coworkers[34,35] made the chiral side-chain portion first and then attached it to the steroidal nucleus. Starting with optically pure (*R*)-(+)-citronellic acid, the acid **19** of high purity was obtained which was converted into the phenyl-sulphone **20**. The aldehyde **21** was obtained from stigmasterol through a series of steps. Addition of **21** to the carbanion derived from **20**, followed by acetylation, Na-Hg reduction and deprotection gave **22**. The acetate of **22** was epoxidised, the oxirane ring cleaved with HBr in AcOH, the bromoacetate heated with AcOH-H_2O, leading to desired (22*R*, 23*R*)-tetracetoxy ketone. The latter was treated with CF_3CO_3H, and hydrolysed to give brassinolide (**1**). Alternatively[36], the aldehyde **21** has been used to prepare brassinolide (**1**) using the sequence developed earlier for design of the side chain[29].

Starting with 60:40 mixture of 22-dehydro-campesterol (**23**) and brassicasterol (C-24 epimer of **23**) from oysters, synthesis of brassinolide (**1**) and its 22*S*,



(13) X=H (14) X=H (15) X=H

(16) X=OH (17) X=OH (18) X=OH



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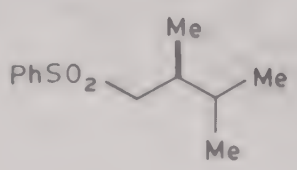

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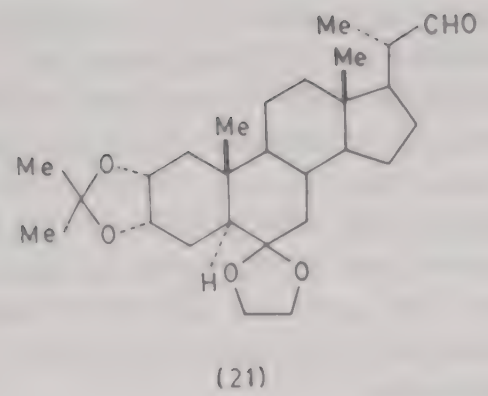

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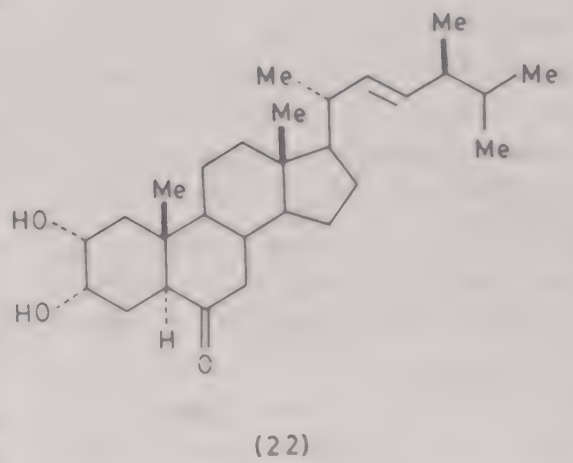

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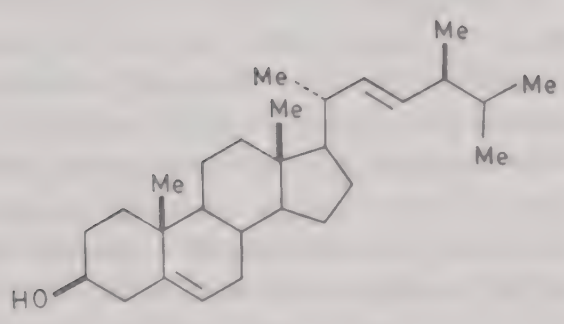

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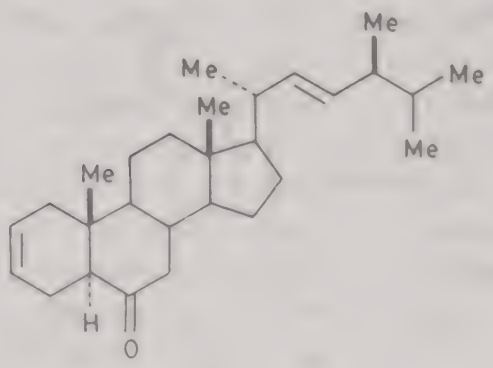


(24)

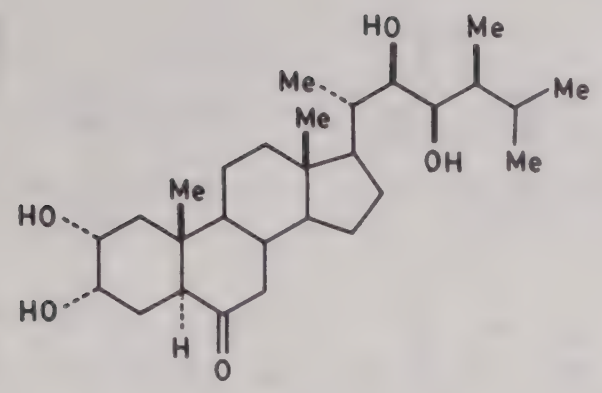
23*S*-isomer has been carried out[37]. Compound **24** was the common intermediate. Osmium tetraoxide treatment gave the 2α, 3α, 22*R*, 23*R*- and 2α, 3α, 22*S*, 23*S*-tetrahydroxy-6-ones which were separated and converted into the tetraacetates. The latter on Baeyer-Villiger oxidation, saponification, followed by acidification gave **1** and the 22*S*,23*S*-isomer, respectively.

Other Natural Brassinosteroids

There is a possibility of ubiquitous presence of brassinosteroids in plant kingdom. The brassinolide related steroids which have been found to occur naturally are discussed in the sequel.

Castasterone and typhasterol

Castasterone (**25**), a 6-oxo steroid related to brassinolide (**1**), was originally isolated in 95 μg quantity from 40 kg of the insect galls of the chestnut tree (*Castanea* spp)[38]. In rice-lamina inclination test it was estimated to be half to quarter as active as **1** over the concentration range between 0.0001 ppm and 0.01 ppm. Castasterone was considered to be of plant origin, since the extract of the larvae collected from the



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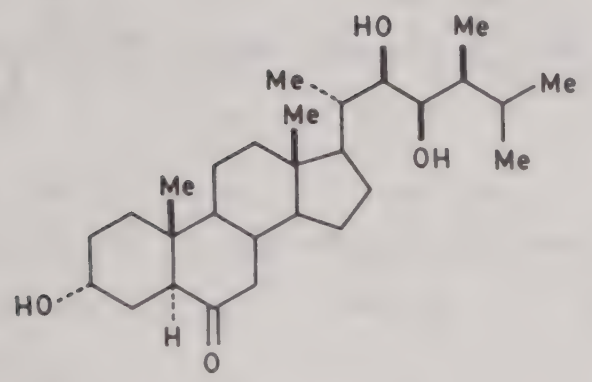

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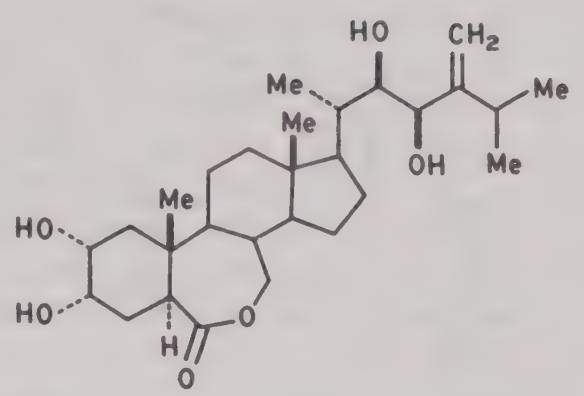

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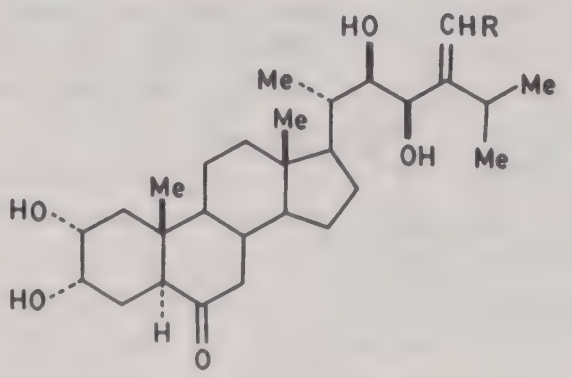


(28) R = H

(29) R = Me

gall tissues had not shown activity in the rice-lamina inclination test[39]. In addition to chestnut galls[14,38] the presence of castasterone has been noted in immature seeds and sheaths of Chinese cabbage (*Brassica campestris* var *perkinensis*)[11,40] leaves of green tea (*Thea sinensis*)[13], *Dolichos lablab*[41], *Phaseolus vulgaris*[42], *Oryza sativa*[43] and *Distylium racemosum*[40].

Typhasterol (2-deoxycastasterone) (**26**) has been isolated in 1.7 mg quantity from 25 kg of cat-tail pollen (*Typha latifolia* Linn)[44]. It is active in rice-lamina inclination test. Castasterone and typhasterol have been isolated from the pollen of Japanese black pine (*Pinus thunbergii*)[45] and they have been identified in extracts from the shoots of Sitka spruce (*Picea sitchensis*)[46].

Castasterone and typhasterol may have their own physiological functions in plant tissues. They are also of biosynthetic interest. From the structural point of view, castasterone may be regarded as a precursor of brassinolide.

Syntheses of castasterone[29,36,37,47] and typhasterol[29] have been reported.

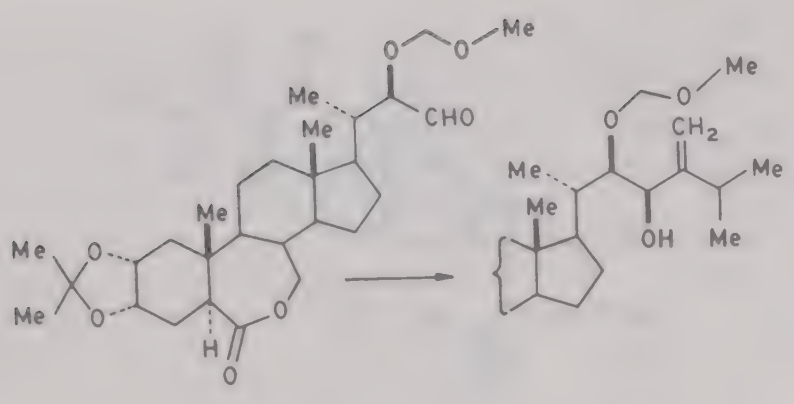
Dolicholide and dolichosterone

From the seeds of *Dolichos lablab*, a new plant growth promoter dolicholide has been isolated (160 mg from 34 kg of seeds) and assigned the structure as (22*R*, 23*R*)-2α,3α,22,23-tetrahydroxy-*B*-homo-7-oxa-5α-ergost-24(28)-en-6-one (**27**)[48]. The biological activity of dolicholide in the rice-lamina inclination assay is about one-tenth of that of brassinolide (**1**). The occurrence of the related 6-ketone (**28**) named dolicholesterone which may be a precursor to **27**, and (22*R*, 23*R*)-2α,3α,22,23-tetrahydroxy-5α-stigmast-24(28)-en-6-one (homodolichosterone) (**29**) in *D. lablab* seeds has also been reported[49].

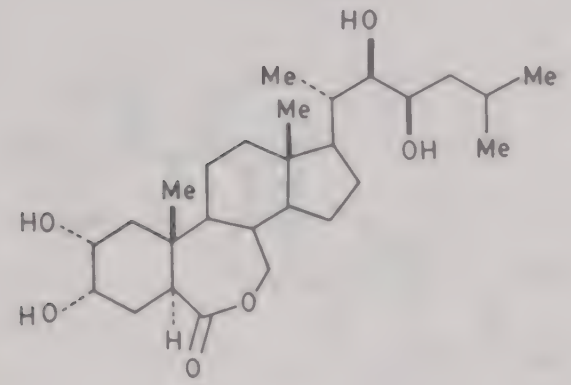
Synthesis of dolicholide and dolichosterone has been carried out[50,51]. First, A,B-ring system was functionalised and then the side-chain part was constructed using the chelation-controlled Grignard reaction of α-hydroxy aldehydes[52,53]. For example, the aldehyde **30**, derived from (22*E*,24*S*)-2α,3α-diacetoxy-5α-stimast-22-en-6-one, on reaction with the Grignard reagent derived from 2-bromo-3-methyl-1-butene in THF at −78°C afforded, exclusively, the (22*R*, 23*R*)-22,23-vicinal dio 22-methoxymethyl ether **31**, whose 23*R* stereochemistry was assigned from the prediction reported by Still[52,53]. From **31** through a sequence of simple reactions, dolicholide (**27**) was obtained.

Brassinone, (24*S*)-24-*ethylbrassinone and* 28-*norbrassinolide*

Three new brassinosteroids, 28-norbrassinolide (**32**), its corresponding 6-ketone named brassinone (**33**) and the analogue (24*S*)-24-ethylbrassinone (**34**) have been identified in Chinese cabbage, in green tea and in chestnut insect galls[54]. The amounts of brassinone (**33**), (24*S*)-24-ethylbrassinone (**34**) and 28-norbrassi-



(30) (31)



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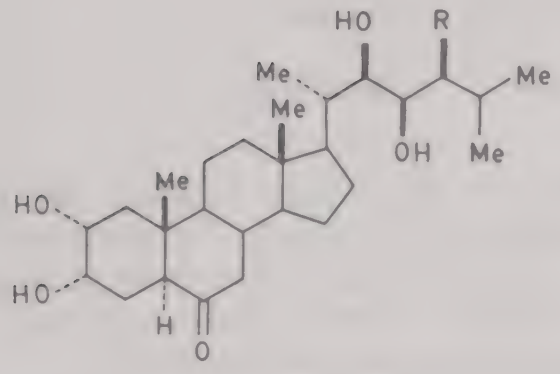
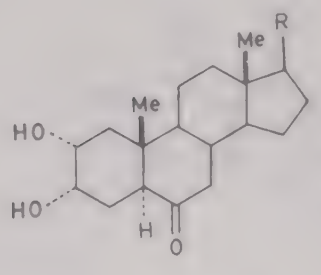
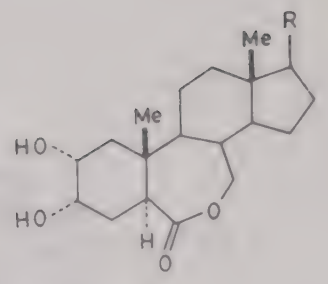


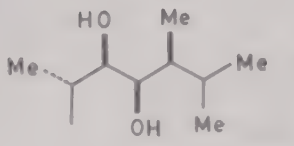
(33) R = H

(34) R = CH_2CH_3

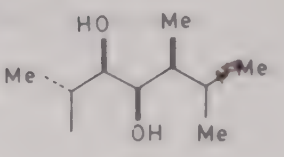




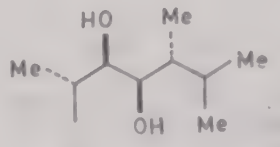
(25) R =



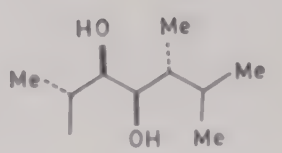
(1) R =



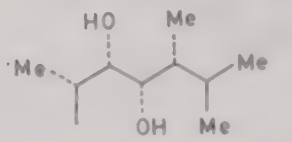
(35) R =



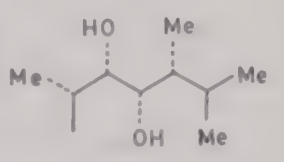
(38) R =



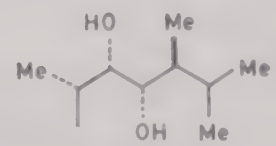
(36) R =



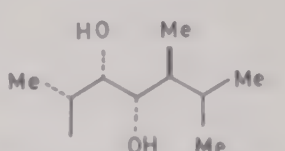
(39) R =



(37) R =



(40) R =



nolide (**32**) in Chinese cabbage (320 kg) were 250 ng, 40 ng and 400 ng, respectively, compared with 3 μg of brassinolide. On the other hand the amounts of **33** and **34** in green tea (65 kg) were 130 ng and 30 ng, respectively; in this plant castasterone (**25**) (7.2 μg) is a major brassinosteroid. In the chestnut insect galls (3.5 kg) the amount of **33** (40 ng) was approximately equal to that of castasterone. In rice-lamina assay, **34** showed activity nearly equal to that of castasterone (**25**) but several times lower than that of brassinolide (**1**). The activity of **33** was equivalent to that of **32** or somewhat weak, being about one-tenth that of **34**. In *Raphanus* test 28-norbrassinolide (**32**) was as active as brassinolide and in the tomato test the activity was one-tenth[21]. In the tests brassinone (**33**) showed much weaker activity.

A probable precursor of brassinolide (**1**) and other related compounds is 24-methylenecholesterol or campesterol. As sitosterol and cholesterol are widely distributed in the plant kingdom, the occurrence of (24*S*)-ethylbrassinone (**34**), brassinone (**33**) and 28-norbrassinolide (**32**) is not unexpected. Brassinone (**33**) may be a biosynthetic precursone to 28-norbrassinolide (**32**).

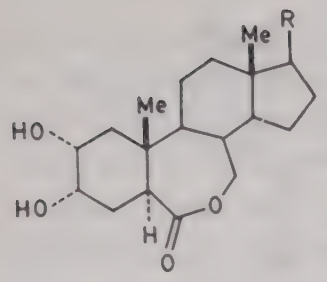
The synthesis of 28-norbrassinolide (**32**)[29,50,55] and brassinone (**33**)[29] has been reported.

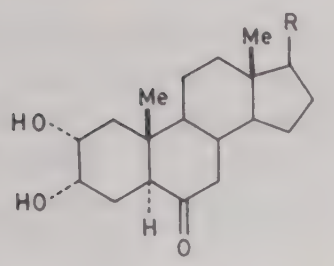
Synthetic Brassinosteroids

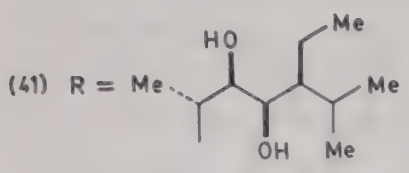
Several synthetic modifications have been carried out on the structures of brassinolide (**1**) and castasterone (**25**). The methodologies developed for the synthesis of these compounds have been of help in the design of the congeners. There has been a focus on the changes in the chiral characters at positions 22, 23 and 24 of the side chain. The preparation of 28-homo derivatives with and without steric modifications in the side chain and changes in the steroid nucleus have also been of interest. There have been obtained analogues having lesser number of carbons in the side chain, and in some relations the polar hydroxyls at positions 22 and 23 are absent. The biological data on many of the synthetic brassinosteroids are available.

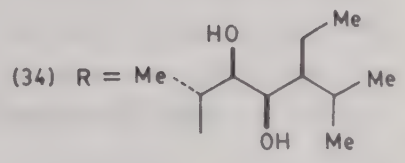
Brassinolide and castasterone isomers with changes configurations at C-22, C-23 and C-24

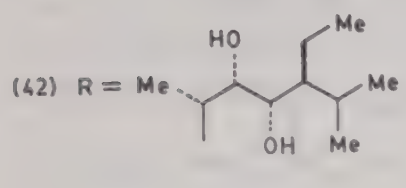
Brassinolide (**1**) and castasterone (**25**) are ergostane derivatives with 22*R*,23*R* and 24*S* configurations. The

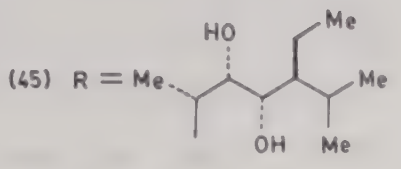


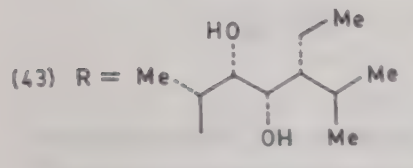


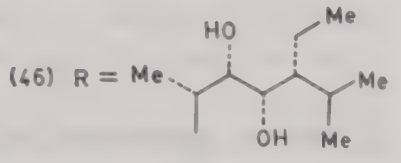


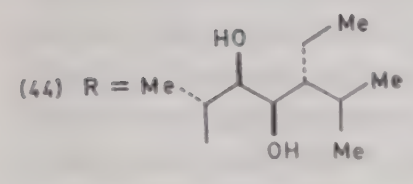


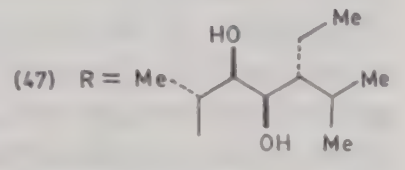












first change made was in the stereochemistry at position-24. Starting with ergosterol, the 22*R*, 23*R*, 24*R*-(**35** and **38**) and 22*S*,23*S*,24*R*-(**36** and **39**) analogues of castasterone and brassinolide were synthesised[56]. The glycol systems were introduced by reacting 5α-ergosta-2,22-dien-6-one with osmium tetroxide, giving 1:1 mixture of the tetrahydroxy ketones (**35** and **36**). The Baeyer-Villiger oxidation of the tetraacetates of **35** and **36** was carried out with *m*-chloroperbenzoic acids giving predominantly the tetracetoxy-*B*-homo-7-oxa-5α-6-ones. The structures of **38** and **39** were confirmed by X-ray diffraction analysis.

The (22*S*,23*S*,24*S*)-isomers **37** and **40** were prepared using 60:40 mixture of 22-dehydrocampesterol (**23**) and brassicasterol (C-24 epimer of **23**) obtained from oysters[37]. Syntheses of (22*R*,23*R*,24*R*)-(**35** and **38**) and (22*S*,23*S*,24*R*)- (**36** and **39**) compounds from brassicasterol have been described[57,58].

Castasterone (**25**) and (22*S*,23*S*,24*S*)-isomer **37** from (20*S*)-6β-acetoxy-3α,5-cyclo-5α-pregnane-20-carbaldehyde has been reported[47].

In the bean second-internode bioassay, the (22*R*,23*R*,24*R*)-(**38**) and (22*S*,23*S*,24*R*)- (**39**) isomers elicited the same responses at about 10 times the concentration of brassinolide (**1**)[37,59]. The compound **38** was slightly more active than **39**. The least active was the (22*S*,23*S*,24*S*)-isomer (**40**). In the bean first-internode bioassay, an auxin-induced growth test system which employs isolated bean plant segments, the isomer **39** caused a greater response than brassinolide. The ketones **25** and **35** showed biological activity in both the tests. **25** was more active than **35** and active as the lactones **38** and **40**. The ketone **36** showed no brassin activity[56].

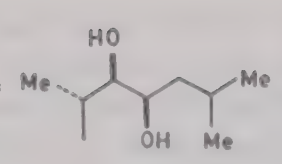
In the *Raphanus* test the (22*S*,23*S*,24*R*)-isomer (**39**) was as active as brassinolide (**1**) and more active than **38**[21]. However, the relative activity was reversed in the tomato test. In the rice-lamina inclination test, the activity of **38** was one-tenth of that of brassinolide, and **39** was less active than **38**[60].

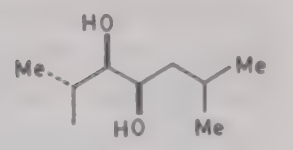
Brassinosteroids with other modifications

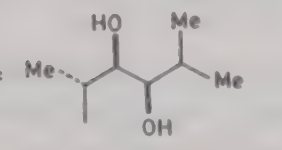
There has been interest in the homo, nor, related stereochemical, and other changes in the side chain, and there have also been made modifications in the steroid nucleus part.

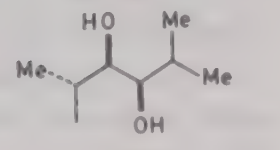
28-Homobrassinolide, chemically named (22*R*,23*R*,24*S*)-2α,3α,22,23-tetrahydroxy-*B*-homo-7-oxa-5α-stigmastan-6-one (**41**), having same side chain configurations as in brassinolide (**1**), has been synthesised starting with stigmasterol[59,61–63]. The C-24 configuration of the stigmasterol side chain remains unaffected. The intermediate (22*E*,24*S*)-3β-hydroxy-5α-stigmast-22-en-6-one was epoxidised, followed by *trans* ring-opening of the resulting epoxdises by HBr-AcOH, then inversion at the carbon bearing bromine by acetoxy anion to give (22*R*,23*R*,24*S*)-3β,22,23-triacetoxy-5α-stigmastan-6-one, which was used to obtain **41**[63]. For preparation (22*S*,23*S*,24*S*)-homobrassinolide (**42**), the respective (22*E*,24*S*)-stigmast-22-ene derivatives were reacted with osmium tetroxide[35,59,64,65]. To confirm the stereochemistry of the side chain, X-ray diffraction analysis of the intermediate (22*S*,23*S*,24*S*)-2α,3α,22,23-bisisopropylidenedioxy-5α-stigmastan-6-one was carried out[35]. The synthesis of (22*S*,23*S*,24*R*)-(**43**) and (22*R*,23*R*,24*R*)-(**44**) 28-homobrassinolides has been achieved starting with poriferasterol (24-epimer of stigmasterol)[60]. The 6-keto analogues **34**, **45**, **46** and **47**, corresponding to the ring-B lactones **41**, **42**, **43** and **44**, respectively, have been obtained while preparing the latter compounds. The occurrence and synthesis of 28-norbrassinolide (**32**) and its corresponding 6-ketone (brassinone) (**33**) has been discussed somewhere else in the paper. The other modifications in the side chain which have been carried out include the preparation of 26,27-bisnorbrassinolide (**48**) and its 6-ketone analogue (**49**)[66], and the analogues **50**-**59**[59].

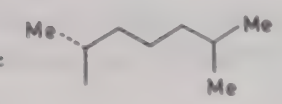
28-Homobrassnolide (**41**) is as highly active as brassinolide (**1**) even at a concentration of 0.0001 ppm in the rice-lamina inclination test[60]. The (22*S*,23*S*,24*S*)-isomer (**42**) is half as active as **41**. The analogues **43** and **44** are much less active and have one-

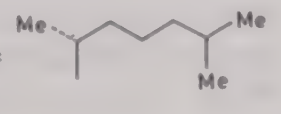
(32) R = 

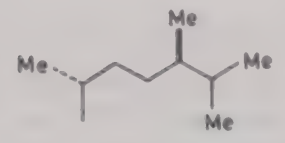
(33) R = 

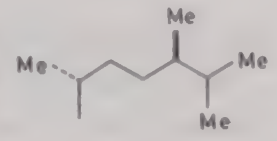
(48) R = 

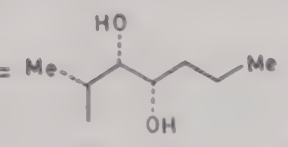
(49) R = 

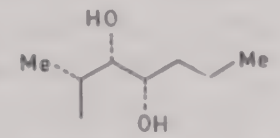
(50) R = 

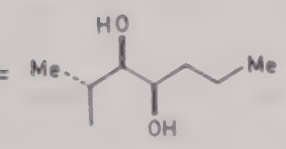
(55) R = 

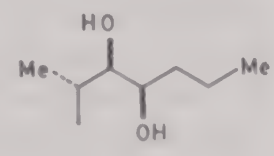
(51) R = 

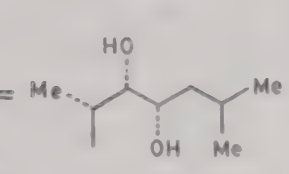
(56) R = 

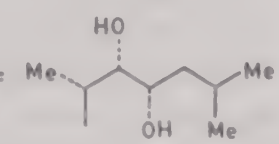
(52) R = 

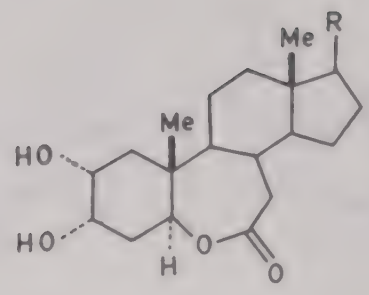
(57) R = 

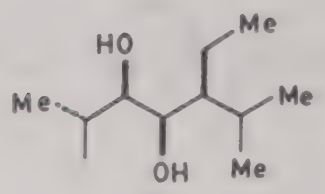
(53) R = 

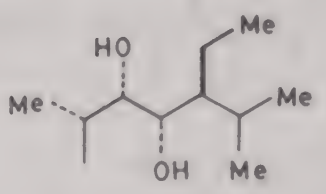
(58) R = 

(54) R = 

(59) R = 



(60) R = 

(61) R = 

twentieth and one-tenth the activity, respectively, as compared with that of **41**. The tetrahydroxy-6-ketone (**34**) has about 50% of the activity of brassinolide and is as active as **25**. The 6-ketones **45**, **46** and **47** show very weak activity. The 28-norbrassinolide (**32**) is less active than **44**. The ketone **33** is weak in activity, and the isomer **59** is even weaker.

It may be noted that activity of 28-homobrassinolide (**41**) in *Raphanus* and tomato tests is much less than that of brassinolide[21]. The 6-oxobrassinosteroids are generally much less active. In *Raphanus* and rice-lamina inclination tests 26,27-bisnorbrassinolide (**48**) exhibits almost the same activity as brassinolide[66]. The 6-keto analogue (**49**) also shows 10-50% of the activity of brassinolide.

In the bean second-internode bioassays, compounds without hydroxyl groups in their side chain (**50** and **51**) are relatively inactive[59]. Except for **52** those brassinosteroids with *cis* hydroxyl groups in their side chain but without an alkyl substituent at C-24 elicit a weak response. In the test **41** and **42** show low activity, **41** being more active of the pair. The tetrahydroxy ketones are generally less active.

Taking 28-homobrassinolide (**41**) as a model several modifications have been carried out in the rings A and B[63]. In the rice-lamina inclination test, the isomeric 6-oxa lactone (**60**) is about one-hundredth as active as **41**. The isomer of **41** having 3α,4α-dihydroxy system rather than the 2,3-glycol function shows about one-half the activity of **41** and 2-deoxy analogues of **41** and **34** show one-tenth the activity of **41**. The other rings A and B modified analogues prepared retain the activity to the extent of 1-10%. Earlier, in the bean second-internode assay it has been shown that **61**, which is a (22*S*,23*S*,24*S*)-isomer of **60**, is inactive[59]. The 2β-OH, 3β-OH isomer of **42** is also not biologically active.

Structure-activity relationship

Though there are variations in the activities in certain cases depending upon the bioassay systems employed some broad structure-activity relationships are evident. 28-Homobrassinolide (**41**) is as active as brassinolide (**1**) in rice-lamina inclination test but in the *Raphanus* and tomato tests the former is much less active. Both **1** and **41** have 22*R*, 23*R*, 24*S*-configurations. The changes in the configurations at these locations lower the activity; some of the stereochemical isomers are fairly active. A methyl or an alkyl group at C-24 is not a must for activity. Dolicholide (**27**), 24(28)-dehydro derivative of brassinolide, retains one-tenth the activity of brassinolide. The analogue 28-norbrassinolide (**32**) has similar activity. Even the still lower homologue, 26,27-bisnorbrassinolide (**48**) has good activity. The changes in the side chain carbon skeleton of brassinolide may be permissible to a good extent. However, 22, 23-vicinal diol, preferably 22*R*, 23*R*, system seems to be essential for the activity.

The *B*-homo-7-oxa-5α-6-oxo lactone system is required for the activity. The *B*-homo-6-oxa-5α-7-oxo lactone isomer **60** of **28** homobrassinolide (**41**) has very

weak activity. The 5α-6-ketones have reduced activity than the respective *B*-homo-7-oxa-5α-6-oxo lactones. Castasterone (**25**) is half to quarter as active as the corresponding lactone brassinolide (**1**). (24*S*)-24-Ethylbrassinone (**34**) related to 28-homobrassinolide (**41**) is nearly as active as castasterone.

The 2α,3α-glycol system is needed for the activity. The 3α,4α-dihydroxy isomer is only half as active as 28-homobrassinolide (**41**), which has 2α,3α-vicinal diol function. The 2-deoxy analogues of 28-homobrassinolide and (24*S*)-24-ethylbrassinone (**34**) show only one-tenth the activity of **41**. Typhasterol (2-deoxycastasterone) (**26**) is active. The removal of 2α-OH lowers the activity but does not completely abolish it.

Summary

The isolation of plant growth promoter brassinolide (**1**) is a discovery of major interest. The *B*-homo-7-oxa-5α-6-oxo lactone system, 2α,3α,22,23-tetrahydroxy functions and the 22*R*, 23*R*, 24*S*-configurations are important structural features for its activity as plant growth promoter. There is a possibility of ubiquitous presence of brassinolide and related compounds, termed as brassinosteroids, in plant kingdom. The prominent naturally occurring brassinosteroids are castasterone (**25**), 6-ketone corresponding to brassinolide; typhasterol (2-deoxycastasterone) (**26**); dolicholide (**27**); 24(28)-dehydro brassinolide; 28-norbrassinolide (**32**); and brassinone (**33**) and the analogue (24*S*)-24-ethylbrassinone (**34**). Methods for the synthesis of brassinolide and several related compounds have been developed. Several synthetic modifications have been carried out in the structures of brassinolide and castasterone, including changes of configurations at C-22, C-23 and C-24, and preparation of congeners with homo, nor and other changes in the side chain and alterations in the rings A an B system. The synthetic brassinosteroid 28-homobrassinolide (**41**) is as active as brassinolide in certain bioassays. A study of brassinolide, 28-homobrassinolide and related compounds show certain structure-activity relationships.

In the years to come there is going to be a continued interest in investigations on the chemistry, structure-activity correlations, biogenesis and practical applications of brassinosteroids. The preliminary studies made so in agriculture have given promising indications.

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Communications

Aureolic Acid Group of Antibiotics: A Stereospecific Synthesis of Side Chain of Aglycone†

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A stereospecific synthesis of the side chain (**4**) present in the aureolic acid group of antibiotics, starting from a D-glucose derivative (**5**) is described.

Olivin (**1**) and chromomycinone (**2**) are the tricyclic aglycones of aureolic acid group of antibiotics with an asymmetric acyclic side chain. Synthetic interest[1] in these molecules arose because of their complex structure coupled with their promising antineoplastic activity[2]. We embarked on the synthesis of **1** and **2** and their retrosynthetic analysis (Scheme 1) revealed that compound **4** would be an ideal key intermediate[3] in the total synthesis of these molecules. In this communication is described a simple and stereospecific synthesis of **4** starting from a D-glucose derivative (**5**), as outlined in Scheme 2.

Methylation of **5** led to the known[4] 3,4,6-tri-O-acetyl-2-O-methyl-1-deoxy-1-piperidino-β-D-glucose (**6**). Subsequent hydrolysis of piperidino group in **6** followed by Zamplen deacetylation resulted in 2-O-methyl-D-glucose which on treatment with methanolic hydrogen chloride under reflux afforded **7**. Treatment of **7** with α,α-dimethoxytoluene in acetonitrile containing catalytic amount of toluene-*p*-sulfonic acid led to a 7:3 mixture of α- and β-glycosides (**8** and **9**). Column chromatography of the mixture yielded pure **8** and **9** in an overall 87% yield.

The α-isomer (**8**) [m.p. 173°, $[\alpha]_D$ +97° ($CHCl_3$)] was treated with NaH-BnBr to give the benzyl ether (**10**) [m.p. 111°, $[\alpha]_D$ +29° ($CHCl_3$)] in almost quantitative yield. The benzylidene group was deprotected with aq acetic acid on a boiling water-bath to give the diol (**11**) which without isolation was transformed into the dimesylate derivative (**12**). Reduction of **12** with lithium aluminium hydride in refluxing THF led to **13** [$[\alpha]_D$ +60.5° ($CHCl_3$)].

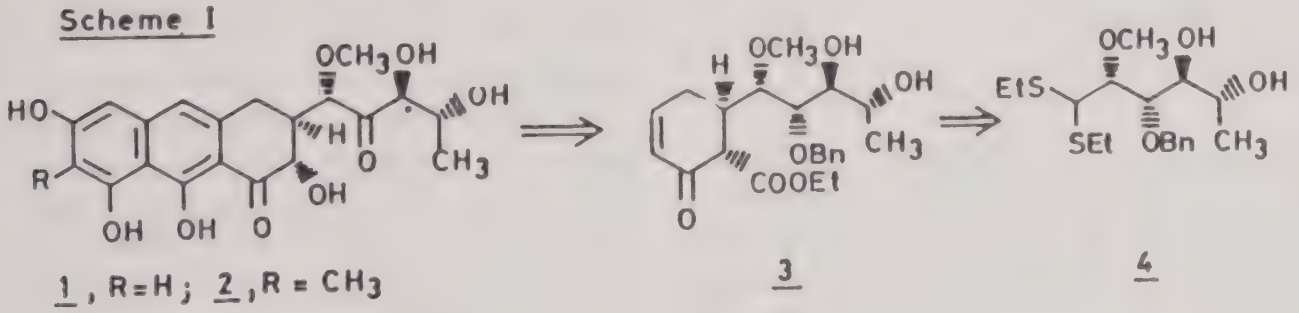
The 'synthon' **13** has all the groups with the absolute stereochemistry as are present in the side chain in **1** and **2** except for the C-4 hydroxyl group whose configuration has to be inverted. This was achieved by oxidation-reduction procedure. For example, **13** was oxidised with PCC-CH_2Cl_2 under reflux to afford **14** which on reduction in the presence of $NaBH_4$-MeOH gave the required alcohol (**15**) [$[\alpha]_D$ +110.6° ($CHCl_3$)] together with the starting alcohol (**13**) in the ratio of 94:6 as revealed by gas chromatography and separation by column chromatography. This was not unexpected since the C-methyl and O-benzyl groups adjacent to the keto group are projected above ('β'-phase) and the delivery of the hydride ion occurs from the 'α'-phase.

An identical series of reactions on 4,6 O-benzylidene-2-methoxy-3-benzyloxy-β-D glucopyranoside (**9**) [m.p. 179-82°; $[\alpha]_D$ −69.67° ($CHCl_3$)] led to the corresponding galacto derivative (**16**).

Deglycosidation of **15** and **16** in the presence of trifluoroacetic acid/water and treatment of the resulting hemiacetal with $EtSH/CH_2Cl_2/HCl/0°C$ gave the open chain diol **4** ($[\alpha]_D$ −3.27° ($CHCl_3$)). The substituents present in **4** were rightly aligned with the side chain of **1** and **2**.

Further work on building up the cyclohexanone portion of **1** and **2**, is in progress.

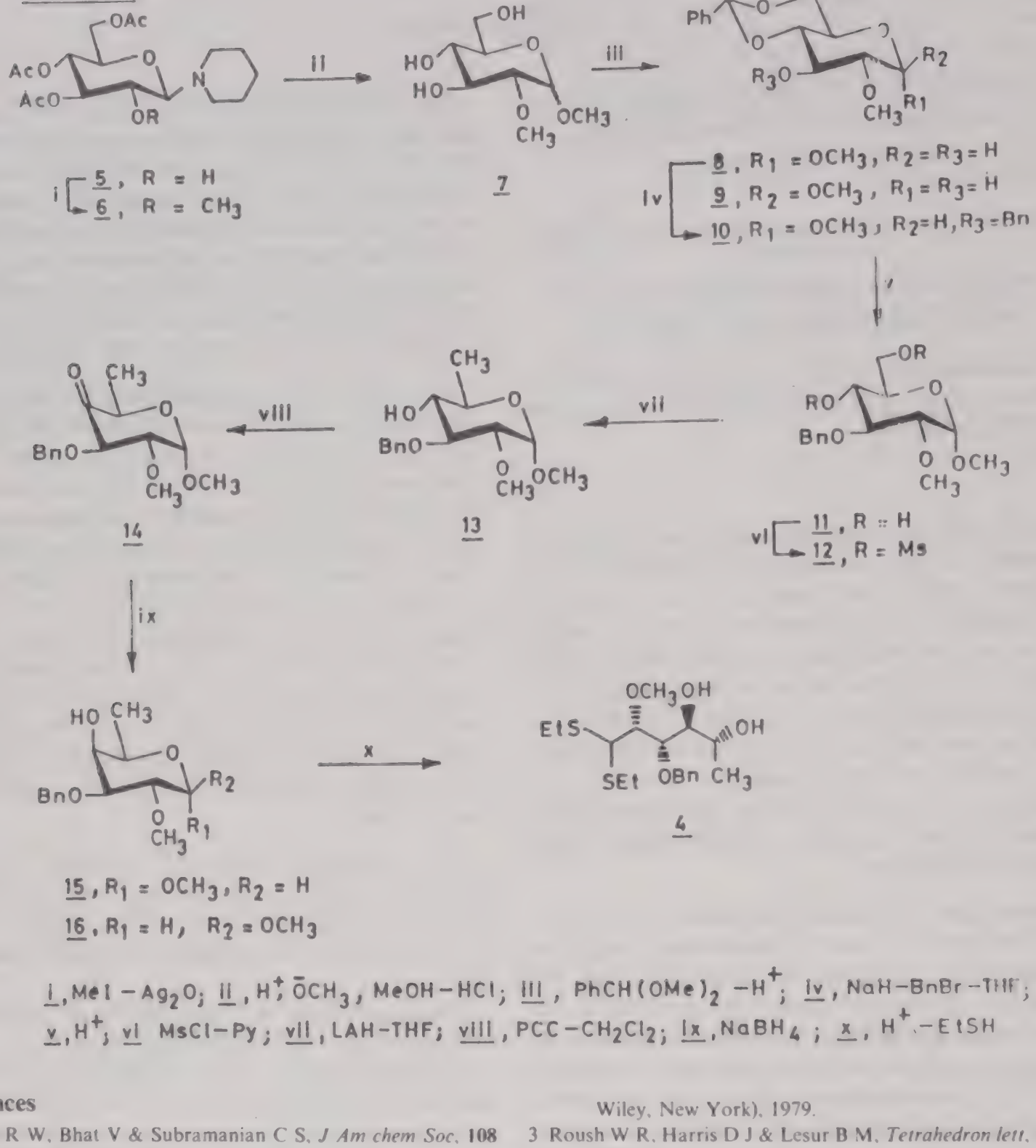
Scheme 1



1, R=H; 2, R = CH_3 3 4

†This work was carried at the National Chemical Laboratory, Pune 411008. NCL communication no. 4041.

Scheme II



i, MeI – Ag_2O; ii, H^+, $\bar{O}CH_3$, MeOH–HCl; iii, $PhCH(OMe)_2$ – H^+; iv, NaH–BnBr–THF; v, H^+; vi MsCl–Py; vii, LAH–THF; viii, PCC – CH_2Cl_2; ix, $NaBH_4$; x, H^+, –EtSH

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Structure & Stereochemistry of Herbacin, a New Furanosesquiterpene from the Marine Sponge *Dysidea herbaceae*

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The Indian variety of the sponge *Dysidea herbaceae* elaborates a furanosesquiterpene (yield 1.3% of dry weight of sponge), designated as herbacin which has been assigned the stereostructure (I), based on spectral data (UV, IR, PMR and CMR and NOE difference spectroscopy).

Dysidea herbaceae is a prolific sponge, occurring in coastal waters of different seas. A variety of novel metabolites like polybrominated diphenyl ethers, polychlorinated amino acid derivatives and sesqui-, di- and sester-terpenes have been reported in literature from this organism. The occurrence of such diverse compounds reflects the influence of ecological conditions on the chemical constituents[1]. Chemical examination of the sponge from Indian shores has not been reported so far. In this communication we report the isolation and structure elucidation of herbacin, a furanosesquiterpene, from the Indian variety of the sponge in good yield (1.3% of dry weight of sponge). Furanosesquiterpenes, in general exhibit antifeedant activity. Herbacin, therefore, assumes importance in this context.

The sponge, *D. herbaceae*, collected during the last week of September, 1983, was shade-dried after washing with water followed by methanol (200 g, dry weight) and extracted in a soxhlet with *n*-hexane. The crude residue (6.8 g) was subjected to column chromatography over silica gel. Elution with *n*-hexane afforded in the early fractions, compound A (2.4 g), m.p. 40-41° (benzene, colourless needles), GLC, single peak (OV-1, 200°, N_2 carrier gas), $[\alpha]_D$ +9.2° (*c*, 0.2, $CHCl_3$), $C_{15}H_{20}O$ (M^+ 216, 16%). It gave a positive Erhlich colour reaction for a furan moiety, and exhibited in the UV spectrum in MeOH maximum absorption at 225 nm (ε, 8000) while its IR spectrum as thin film displayed peaks at 3020, 1500, 870 and 740 cm^{-1}, thus supporting the presence of a furan moiety[2] in the molecular framework of compound A. Its PMR spectrum (400 MHz, C_6D_6) revealed that the furan moiety was 2,3-disubstituted (δ 7.11, *d*, J = 2 Hz, 12-H; 6.00, *d*, J = 2 Hz, 11-H)[3].

The compound is thus a furanosesquiterpene, containing in addition, an isolated 1,2-disubstituted double bond (δ 5.90, *dt*, J = 10, 2 Hz, 1-H; 5.58, *dt*, J = 10, 3 Hz, 2-H). Its sp^2 carbons (δ 131.6, *d*, C-1; 125.5, *d*, C-2) together with those of the furan moiety (δ 157.2; *s*, C-9; 140.5, *d*, C-12; 112.8, *s*, C-8; 109.3, *d*, C-11) make up the total complement of six low field carbons in the CMR spectrum (100 MHz, $CDCl_3$, δ; signals of the remaining nine carbons at 40.9, *s*, C-10; 37.9, *s*, C-5; 31.5, *t*, C-7; 29.7, *t*, C-3; 29.6, *d*, C-4; 24.1, *g*, C-13; 18.5, *t*, C-6; 15.8, *g*, C-15 and 15.1, *g*, C-14). The compound also contained three methyls of which two were tertiary (δ 1.22, *s*, 13-Me; 0.70, *s*, 15-Me) and one secondary (0.71, *d*, J = 7 Hz, 14-Me; the corresponding methine, 4-H, appeared as a sextet at δ 1.83, J = 7 Hz). The remaining six protons were distributed in three cyclic methylenes, among which two were allylic (δ 2.26, *ddd*, J = 16, 12, 5 Hz, 7-H_{ax} and 2.17, *ddd*, J = 16, 6, 2 Hz, 7-H_{eq} and 1.62, *m*, 3-H_2), the former being connected to the third high field methylene protons (δ 1.58, *ddd*, J = 13, 12, 6 Hz, 6-H_{ax} and 1.48, *ddd*, J = 12, 5, 2 Hz, 6-H_{eq}). These assignments are based on correlations with known furanosesquiterpenes, notably pallescensin-G[4] and microcionin-1[5] and confirmation having come from decoupling experiments. The J values of different protons are given in Table 1.

Table 1—Coupling Constants of Protons in Structure (I)

Origin	J (in Hz)	Origin	J (in Hz)
1,2	10	4,14	7
1,3 (ax)	2	6(ax), 6(eq)	13
1,3(eq)	2	6(ax), 7(ax)	12
2,3(ax)	3	6(ax), 7(eq)	6
2,3(eq)	3	6(eq), 7(ax)	5
3(ax), 4(eq)	7	6(eq), 7(eq)	2
3(eq), 4(eq)	7	7(eq), 7(ax)	16

From the foregoing, a 1,2-didehydromicrocionin-1 structure is indicated for herbacin (I). Since a full stereochemical structure of microcionin-1 was not proposed[5], that of herbacin has been deduced by NOE-FID difference PMR technique. Such a spectrum (400 MHz, C_6D_6) recorded for I by irradiation of the 13-Me (Fig. 1) displayed signals at δ 5.90 (*dt*, J = 10, 2 Hz, 1-H), 1.58 (*ddd*, J = 13, 12, 5 Hz,

6-H_{ax}; this pattern was discerned by the disappearance of the adjacent and partly overlapping 1.62 *m* of 3-H_2 of the original spectrum) and 0.70 (*s*, 15-Me). Hence, the two angular 13-Me and 15-Me are on the same side of the molecule (i.e., A/B ring junction is *cis*) and are together on the opposite side of 14-Me. A Drieding model with a relative 13β-Me further revealed its closest proximity to 15-Me followed by 6-H_{ax} and 1-H.

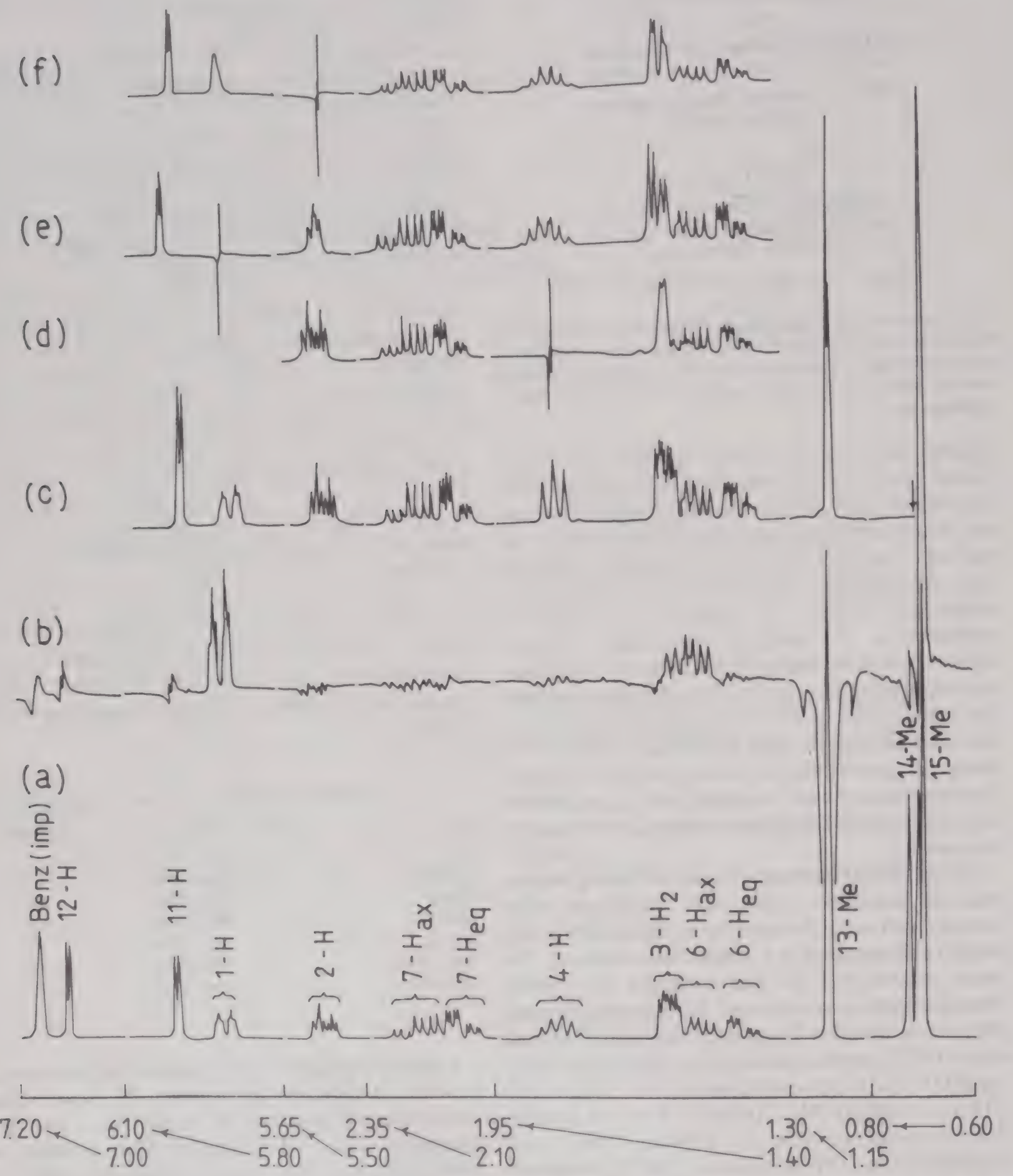
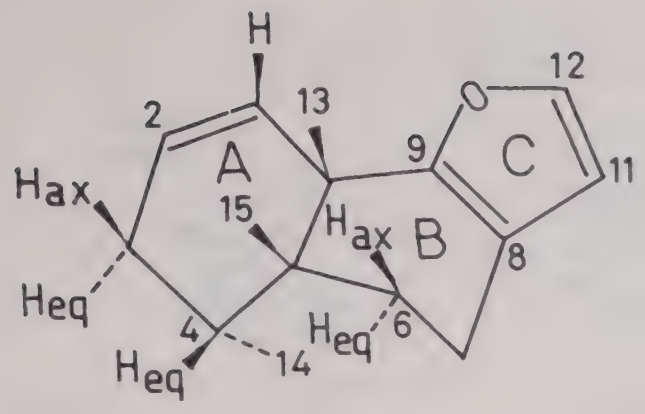


Fig. 1 — 400 MHz PMR spectra of herbacin (I) in the Ranges of δ 0.60 to 0.80, 1.15 to 1.30, 1.40 to 1.95, 2.10 to 2.35, 5.50 to 5.65, 5.80 to 6.10 and 7.00 to 7.20 (no peaks were noticed in other ranges) [(a) Control spectrum, (b) NOE (irradiation at 13-Me) minus FID spectrum; (c) 14-H decoupled spectrum; (d) 4-H decoupled spectrum; (e) 1-H decoupled spectrum; and (f) 2-H decoupled spectrum



I

The authors thank the UGC, New Delhi for a grant and Dr P A Thomas, Vizhinjam R C of CMFRI, Cochin for identification of the sponge. They also thank the Director, NIO, Dona Paula for assistance in the collection of the sponge.

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Electron Transfer Mechanism for Periodic Acid Oxidation of Aromatic Substrates

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Evidence for the involvement of cation radicals during the periodic acid oxidation of aromatic substrates like hydrocarbons, phenolic ethers, phenols etc. has been presented.

Reaction of aromatic substrates with periodic acid presents a complex and somewhat confusing pattern. It has defied adequate mechanistic description[1-3]. The key question is: Are there different mechanisms for the oxidation of aromatic hydrocarbons, phenols and phenolic ethers or a single obligatory pathway with minor variations? We present here the results of experiments which answer this question.

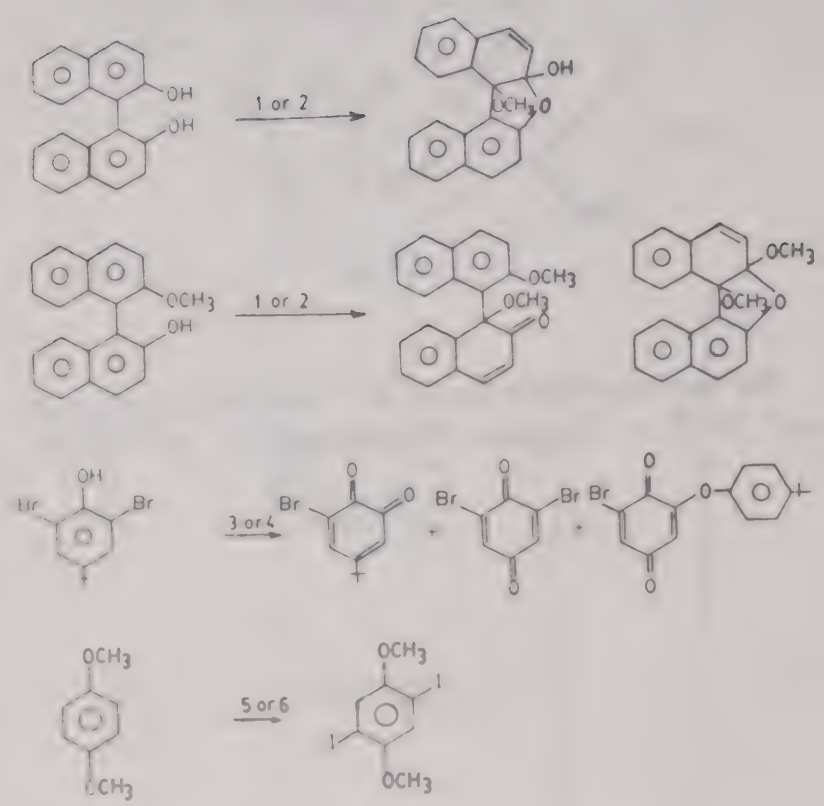
(1) Every aromatic substrate that we have studied, whether it is a polycyclic aromatic hydrocarbon, phenol or phenolic ether, gives ESR signal in appropriate solvent with periodic acid (see Table 1). This includes hydrocarbons like naphthalene, anthracene and phenanthrene which were previously reported[4] not to give the ESR signals[4a].

(2) Reaction of phenols, aromatic hydrocarbons and phenolic ethers involves liberation of a nearly stoichiometric amount of *iodine* in methanol, acetic acid and acetonitrile media. Formation of iodine necessarily involves a redox process.

Table 1—ESR Spectra of Aromatic Substrate-H_5IO_6 System

Aromatic substrate	*g* value
1. 2,6-Dibromo-4-*t*-butylphenol	2.0106[a]
2. 2,2′-Dihydroxy-1-1′-dinaphthyl	2.0031[b]
3. 2-Hydroxy-2′-methoxy-1,1′-dinaphthyl	2.0003[a]
4. Naphthalene	2.0045[c]
5. Anthracene	2.0031[c]
6. Phenanthrene	2.0063[c]
7. 1,4-Dimethoxybenzene	2.0048[c]
8. 1,2-Dimethoxybenzene	2.0034[b]
9. *p*-Methoxytoluene	2.0039[b]
10. *m*-Methoxytoluene	2.0006[b]
11. *o*-Methoxytoluene	2.0037[b]

(a) Aq ACOH, −140°; (b) Aq CF_3-COOH, −140° and room temp.; and (c) Aq CF_3COOH, −140° and room temp.


1 or 2
1 or 2
3 or 4
5 or 6
1) H_5IO_6 / MeOH; 2) CAN / MeOH; 3) H_5IO_6 / CH_3CN / H_2O;
4) CAN / CH_3CN / H_2O; 5) H_5IO_6 / MeOH REFLUX;
6) $K_2S_2O_8$ / $CuSO_4$ / MeOH / I_2 REFLUX.

Scheme 1

(3) The product pattern of periodic acid oxidation and that of single electron oxidants like ceric ammonium nitrate[5] and potassium persulphate[6] in the presence of copper sulphate are essentially the same in all the cases examined (see Scheme 1). Yields in both the sets of experiments were comparable.

(4) Phenolic ethers give iodinated products and the side chain-oxidised products, the formation of which is inconsistent with the electrophilic attack mechanism[4] for hydrocarbons (see Table 2).

(5) A critical review of the literature reveals that there is no direct evidence either for the formation of periodate ester of phenols[7-9], or for the formation of phenoxenium ion.

(6) More nucleophilic benzyl alcohol and phenethyl alcohols give products (Scheme 2) which are incosistent with the periodate ester mechanism.

Benzyl alcohol $\xrightarrow{I}$ benzaldehyde (70%) + 4-iodobenzaldehyde (14%).

Phenylethyl alcohol $\xrightarrow{I}$ benzaldehyde (55%) + 4-iodobenzaldehyde (11%) + 4-iodophenylethyl alcohol (16%).
(I: H_5IO_6 dioxane/H_2O, 100°C)

Scheme 2—Products in the reaction of aromatic alcohols with H_5IO_6.

Table 2—Products in the Reaction of Phenolic Ethers with h_5IO_6[a]

Starting material	Ratio of substrate to oxidant	Conditons	Product	Yield %
1. 1,4-Dimethoxybenzene	1:2	abs. MeOH, 60-70°C, 7 hr	2,5-Diiodo-1,4-dimethoxybenzene[10]	61
2. 1,4-Dimethoxybenzene	1:2	aq. acetic acid, 95-100°C, 8 hr	2,5-Diiodo-1,4-dimethoxybenzene[10]	55
3. 1,2-Dimethoxybenzene	1:2	abs. MeOH, 60-70°C, 10 hr	4,5-Diiodo-1,2-dimethoxybenzene[10]	45
4. *p*-Methoxytoluene	1:1	abs. MeOH, 60-70°C, 8 hr	2-Iodo-4-methyl anisole	68
5. *p*-Methoxytoluene	1:2	abs. MeOH, 60-70°C, 12 hr	3-Iodo-4-methoxy benzaldehyde[11]	66
6. *o*-Methoxytoluene	1:1	abs. MeOH, 60-70°C, 9 hr	4-Iodo-2-methyl anisole[12]	64
7. *o*-Methoxytoluene	1:2	abs. MeOH, 60-70°C, 12 hr	5-Iodo-2-methoxy benzaldehyde[13]	61
8. Nitrobenzene	1:2	abs. MeOH, 60-70°C, 14 hr	No oxidation	
9. *p*-Nitroanisole	1:2	abs. MeOH, 60-70°C, 16 hr	No. oxidation	

(a) The products were characterized by spectroscopic methods and by comparison of m.p. with literature m.p.

These observations and a large amount of data in the literature[1-3] pertaining to the formation of dimeric and polymeric products are consistent only with the following view. The primary process in the reaction of periodic acid with different aromatic substates involves a single electron transfer to form the cation radical of the aromatic substrate. This is followed by the loss of a proton in the case of phenols to form phenoxy radicals and disproportionation of I^{+6} species to the lower valent iodine derivatives. The formation of all the observed products could be rationalised on the basis of known pattern of reactivity of cation radicals including further oxidation of the radical species formed from them.

We express our appreciation to the CSIR, New Delhi for the Emeritus Scientist Grant to MVB.

References and Notes

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Papers

Ketosantalic Acid, a New Sesquiterpenic Acid from Indian Sandalwood Oil

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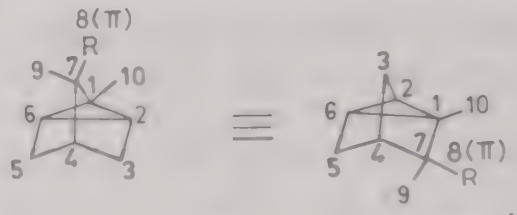
Indian sandwalwood oil contains over one hundred constituents including about fifteen acids, some occurring only in traces. One of these is a new acid, ketosantalic acid (11-keto-dihydro-α-santalic acid, **8**), isolated as its methyl ester (**9**). Its structure has been determined on the basis of spectral and chemical evidences, including its conversion into the γ-lactone (**10**) and the nitrogen-containing compound (**12**), formed via reduction with sodium borohydride and Wolff-Kishner reaction respectively. Products obtained by Beckmann rearrangement of the oxime (**34**) and Wagner-Meerwein Nametkin rearrangement of **9** also provide supporting evidences. **9** is resistant to Baeyer-Williger oxidation. Certain synthetic approaches yield bi-π-tricyclyl (**30**), teresantalol (**26**) and an unsaturated alcohol (**29**). Oxidation of α-santalyl acetate (**37**) with *t*-butyl chromate, instead of yielding the desired 11-keto-α-santalyl acetate (**38**), gives 12-acetoxy-13-keto-nor-α-santalane (**40**), formation of which has been rationalised.

The chemistry of Indian sandalwood oil (*Santalum album* Linn.) has received considerable attention[1-10]. It is known to contain over hundred compounds, the main two being α-santalol (**3**, 70%) and β-santalol (**4**, 20%), having the tricyclene (**1**) and the camphene (**2**) systems respectively. Most of the other constituents of the oil are closely related to or derived from one of these sesquiterpenes. Careful examination (GLC/TLC) has shown that sandalwood oil contains about fifteen acids, some occurring only in traces, either in the free state or as esters. Three of these are teresantalic acid (**5**), nortricycloekasantalic acid (**6**) and tricycloekasantalic acid (**7**). A new acid, ketosantalic acid [11-keto-dihydro-α-santalic acid (**8**); numbering based on the system adopted for camphor (**19**) and tricyclene (**1**)] has now been isolated through a combination of distillation and chromatography of the methyl esters. The structure (**8**) for it was decided on the basis of chemical and spectral evidences (IR, PMR and mass).

Detailed studies carried out earlier[11] have shown that all the compounds containing the tricyclene system (**1**), in which the 8- or π-position is unsubstituted or substituted by various oxygenated or oxygen-free groups, show IR absorptions (values in cm^{-1}) in the region 822, 854, 876 and 3050, which may collectively be considered as safe and typical evidence for the tricyclene and 8(π)-substituted tricyclene systems, as present in **3**, **5**, **6**, **7** and many others.

The similarity of IR spectrum of **9** with that of system (**1**), indicated that it also contained the tricyclene system (**1**) and was closely related to **3**.



1, R = CH_3 ; **3**, CH_2 CH_2OH ;

5, COOH ; **6**, CH_2 COOH ; **7**, CH_2 COOH ;

8, CH_2 COOH ; **9**, CH_2 COOMe

10, ; **11**, CH_2 COOH ;

12, ; **20**, CH_2Br ; **24**, CH_2–O COOMe ;

25, CH_2–O COOMe ; **26**, CH_2OH ;

30, CH_2–CH_2 ; **31**, CH_2–O COOMe

33, CH_2 O COOMe ; **34**, CH_2 NOH COOMe

35, CH_2–NH COOMe ; **36**, CH_2 NH COOMe

Further, in addition it also showed absorptions at 1710 (keto group) and 1735 (ester function). It formed a crystalline semicarbazone, the UV spectrum of which was characteristic of the semicarbazone of a saturated carbonyl derivative[12]. The ester regenerated from the semicarbazone by treatment with dilute acetic acid[13] analysed correctly and had properties as before. Its PMR spectrum was completely consistent with the assigned structure and agreed well with the other well known santalene derivatives.

The parent keto acid (**8**), obtained from **9** by saponification, also showed IR absorptions characteristic of system (**1**). Like all compounds containing this system, **8** and **9** gave faint colouration with tetranitromethane but PMR data (vide Experimental) for most of the compounds, ruled out the presence of any unsaturation.

Reduction of **8** with sodium borohydride or of **9** with the same reagent or with sodium and alcohol gave a crystalline γ-lactone (**10**). It showed IR absorption at 1764 (γ-lactone) and for the tricyclene system. Its PMR spectrum was consistent with the structure.

As such, **9** formed a normal semicarbazone, but Wolff-Kishner reduction of **9** via its hydrazone or the semi-carbazone, instead of yielding the desired dihydro-α-santalic acid (**11**), gave a crystalline nitrogen-containing product (**12**), with the tricyclene system intact (IR). The PMR spectrum was also completely consistent with the structure. The product, presumably, was formed by the elimination of an alcohol molecule from the intermediate hydrazone. Similar behaviour of ketoesters during Wolff-Kishner reduction has been observed earlier[14]. Thus, 2-acetyl-3-carbethoxy-5-methylpyrrole (**13**), when subjected to direct reduction, is converted into a pyridazine (**14**) by the loss of ethyl alcohol from the intermediate hydrazone[15]. In the present case, the formation of **12** was a further proof of the location of the carbonyl function in **9** with respect to the carbethoxy group.

Though the formation of **10** and **12** provided convincing proof for the location of the carbonyl function in **9**, other supporting evidences were also sought. In this context, **9** was subjected to Baeyer-Williger oxidation with excess of perbenzoic acid for prolonged periods with a view to obtaining **31** or **32** which on hydrolysis would give **26** or **16**. However, **9** was resistant to Baeyer-Williger oxidation, probably due to steric hindrance created by the proximity of the bulky tricyclene system or some other unknown reasons.

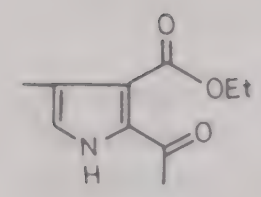
On the other hand, **9** easily formed an oxime (**34**) which on Beckmann rearrangement[16,17] gave an amide (**35** or **36**). Of these, **35** on hydrolysis would furnish methylsuccinic acid, which should give strong fluorescence test, which indeed was the case. The course of the Beckmann rearrangement was, therefore, clear from these findings.

Wagner-Meerwein and Nametkin rearrangements[18,19] involving rearrangement of structures/migration of groups, are common features for compounds containing the tricyclene system. Thus, **7** is known to give **15**, **16** and **17** on treatment with acidic reagents[7–9]. Similarly, when **9** was treated with formic acid, the tricyclene ring system in it was ruptured leading to the formation of four products (GLC/TLC). The product mixture showed IR absorptions for lactone, ester, *gem*-dimethyl, α,β-unsaturated ketone etc. Though of low intensity, UV absorption (λ_{max} 243 nm, ε 961), distinctly suggested the presence of a conjugated carbonyl system, possibly due to the presence of **18**, formation of which is expected. Due to paucity of material isolation of the components in the pure state was not attempted.

Efforts were made to synthesise ketosantalic acid. Though the main objective was not realised, several interesting products were obtained and characterised. In this connection, π(8)-bromotricyclene (**20**), a convenient starting material, was prepared by a known method involving five steps from (+)- and (±)-camphors (**19**)[20–22]. Cadmium-Grignard complex[23,24] of **20** was condensed with the esteracyl-chloride (**21**), but this was not pursued beyond one experiment, as such products are known to isomerise, giving a mixture[25] (**21**, **22**). Therefore, as a matter of preparative convenience and preference, the cadmium complex was condensed with methylsuccinic anhydride[26–29] (**23**). The more polar fraction of the condensation product obtained in low yields gave two peaks (GLC), retention time of one of which was close to that of **9**.

IR and PMR spectra and elemental analyses showed that the product mixture was ester-like in nature and in a portion of the product the tricyclene system had opened giving rise to unsaturation ($C=CH_2$), as present in a camphene-like structure. The two components of the mixture (**24** or **25**) and (**26** or **27**) were separated in the pure state by preparative layer chromatography over silver nitrate-impregnated silica gel[30] as the fast and the slow moving products. The former on hydrolysis yielded the well known alcohol teresantalol (**26**). The latter, on hydrolysis gave an unsaturated, crystalline alcohol, presumably, **29**. A crystalline hydrocarbon, m.p. 117°, which was formed simultaneously in substantial quantity was the interesting compound, bi-π-tricyclyl (**30**), obtained by condensation of two units of π-bromotricyclene with elimination of bromine atoms.

In another synthetic approach, pure α-santalyl acetate (**37**, 97% by GLC), conveniently isolated by a one-step chromatography of sandalwood oil acetate



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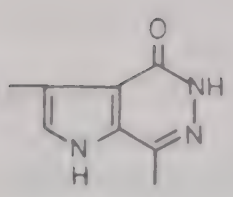

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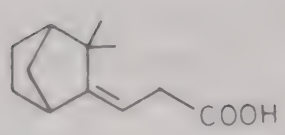

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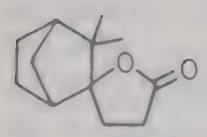

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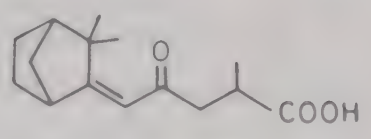

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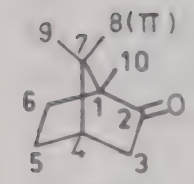

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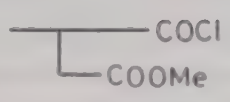

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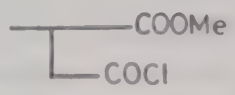

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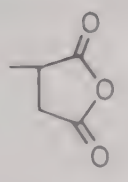

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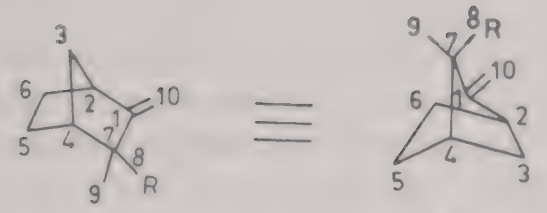


2, R = CH_3 ; 4, CH_2 CH_2OH ;

15, CH_2 $COOH$; 27, CH_2-O $COOMe$;

28, CH_2-O $COOMe$; 29, CH_2OH

mixture on silver nitrate-impregnated silica gel[30], was subjected to allylic oxidation with *t*-butylchromate in carbon tetrachloride[31-33] with a view to obtaining the conjugated ketone, 11-keto-α-santalyl acetate (**38**), for further processing. GLC analysis of the product mixture showed the presence of one major and three minor products, along with some unreacted **37**.

The main product was isolated by chromatography in the pure state (97%). Examination of its properties showed that it was not the desired product **38**, but actually the acetyl derivative of an acyloin, 12-acetoxy-13-keto-nor-α-santalane (**40**), formed, presumably, via acyl migration/partial oxidative cleavage. In conformity with its structure it showed IR absorptions for tricyclene system, isolated keto group (1720) and acetate function (1740). It showed no UV absorption in the region 220-240 nm, gave iodoform test for a methyl ketone and formed a 2,4-DNP derivative which deserves special mention. The nitrogen content (18.78%) indicated that it was not the mono DNP-derivative ($C_{22}H_{28}N_4O$ requires N, 12.6%) of **40** but a bis-DNP-derivative, an osazone (**41**, $C_{26}H_{28}N_8O_8$ requires N, 19.3%), a product, formation of which is characteristic of an acyloin (in the present case formed via hydrolysis of **40**, during derivative formation), a vicinal diketone[34] and reminiscent of the behaviour of carbohydrates[35], hydroxyacetone[36] etc. Apart from the nitrogen-content the derivative showed characteristic UV absorption with three maxima and the appropriate ε values[34].

The PMR spectra of **40**, which merits some discussion was completely consistent with the structure. There was no signal in the vinyl proton region indicating that the trisubstituted double bond in the starting **37** was missing along with the two protons in the α-position to the acetoxy function. Instead, there appeared a signal near δ 2.1 (two overlapping singlets, 6H) and a triplet near 4.85 (1H). These signals, taken together, indicated the presence of a secondary acetoxy group. Another signal near 2.1 was due to a methyl group, the downfield shift suggested that it was in α-position to the carbonyl function. The other features of the PMR spectrum were two cyclopropyl protons (0.83, 2H) and two tertiary methyls (0.83, 1.01).

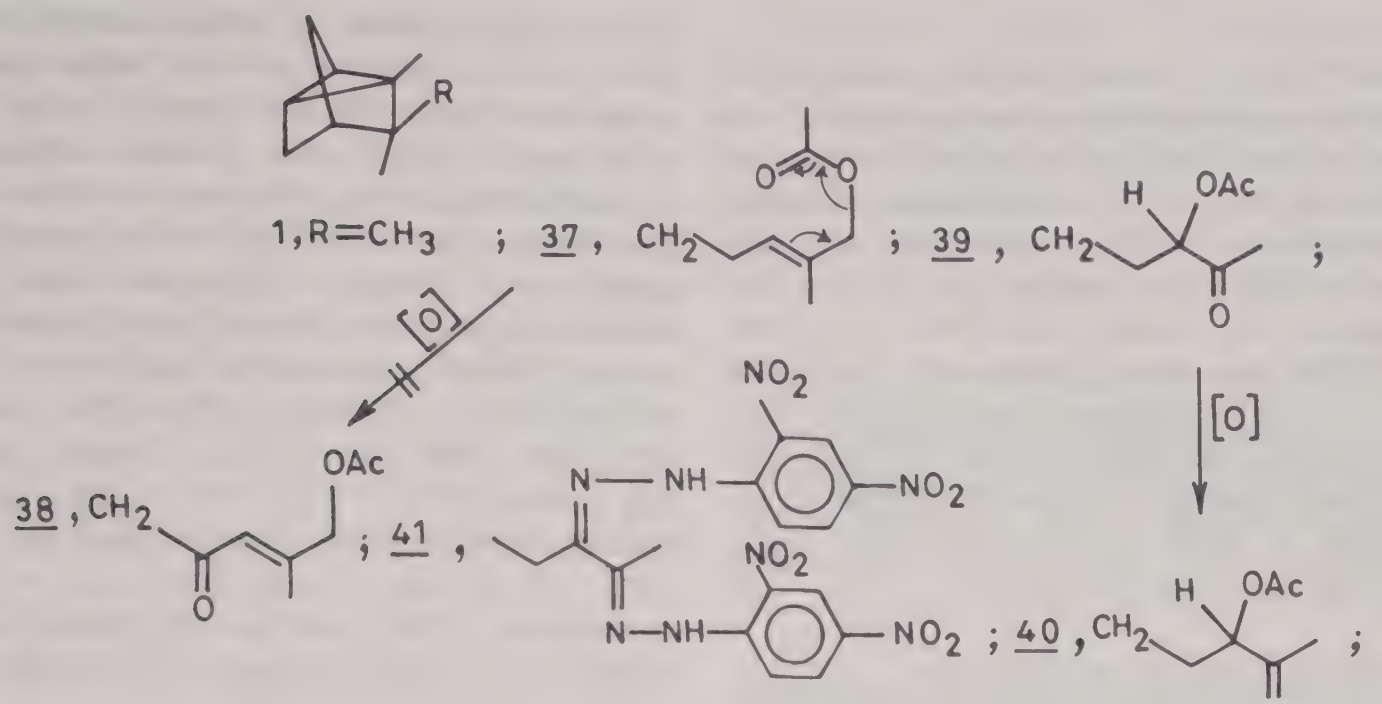
It is difficult to be definite about the genesis of **40**. However, it is felt that under the reaction conditions employed, a kind of reverse allylic rearrangement might be taking place (Scheme 1), leading to the formation of **39**, followed by oxidative cleavage to yield **40**. This abnormal behaviour might be a result of the large size of the reagent and also of the bulky nature of the tricyclene system present in **37**. A somewhat similar situation of the rearrangement of a trisubstituted double bond to a disubstituted one due to steric reason[20] and also the migration of the acyl function to a vicinal carbon atom have been noted earlier[37,38]. No further comments would be justified at this stage.

Experimental Procedure†

Isolation of the acids of Indian sandalwood oil

Treatment of Mysore sandalwood oil (1 kg) with ethanolic potash (2 litres, 2.5%; room temperature 60

†Standard analytical practices and standard instruments manufactured by reputed houses were used for all measurements



Scheme 1

hr; water bath, 1 hr), removal of solvent under reduced pressure, dilution of the residue with water, extraction of the non-acidic portion with pet ether (3 × 500 ml) left the alkaline aqueous layer which on careful acidification in the cold, followed by extraction with ether, washing (water), drying (Na_2SO_4) and subsequent removal of ether gave the acidic portion, which for final purification was redissolved in adequate volume of aqueous alkali, traces of non-acidic portion removed by extraction with ether, the aqueous layer acidified, the reliberated acid extracted with ether, washed (water), dried and processed in the usual way to finally yield the 'total acid' (10 g). GLC showed about 15 peaks, some in traces. TLC showed many spots. Several kilos of the oil were thus processed.

Esterification of the 'total acid': Separation of methyl esters of acids **5** *and* **8** *and isolation of the corresponding free acids*

The acid fraction (10 g) in ether (100 ml) was esterified with diazomethane, prepared from KOH solution (30 ml, 40%) and nitrosomethylurea (10 g). Excess diazomethane was decomposed with acetic acid, the ether layer washed with water, aq Na_2CO_3 (5%), water, dried and the solvent removed to yield the ester; IR: 2950, 1754, 1740 ($-COOCH_3$), 1460; 1380, 1358 (*gem*-dimethyl), 3030, 885, 862, 830 (tricyclene ring system); 790 cm^{-1}.

Isolation of methyl teresantalate and teresantalic acid (**5**)

The total ester (10 g), as obtained above, was chromatographed on silica gel (1:30, activated at 125-50° for 5 hr), eluting with pet. ether (40-60°, 60-80°), pet. ether-benzene, benzene, ether, acetone. The earlier pet. ether, pet. ether-benzene cuts, which contained esters of several lower acids (GLC) were combined and fractionally distilled. The first fraction, b.p. 140-50° (bath)/18 mm, contained essentially methyl teresantalate and was redistilled twice to yield the pure ester, b.p. 150-55° (bath)/20 mm; IR: 3050, 1730, 1455, 1445, 1430, 1370, 1280, 1255, 1180, 1150, 1120, 1075, 1035, 980, 975, 880, 855, 820 cm^{-1} PMR (CCl_4): δ 0.82 (*s*, 2H, cyclopropyl protons), 1.07 (*s*, 3H, C_1-CH_3), 1.22 (*s*, 3H, C_7-CH_3), 3.6 (*s*, 3H, carbomethoxy methyl) (Found: C, 73; H, 8.8. Calc. for $C_{11}H_{16}O_2$: C, 73.3; H, 9.0%).

For the isolation of **5**, methyl teresantalate (0.1 g) and ethanolic potash (1 ml, 4%) were refluxed for $2\frac{1}{2}$ hr on a water-bath. The reaction mixture was cooled, diluted with water and extracted with ether. The alkaline layer was acidified in the cold, extracted with ether, washed with water, dried and the solvent removed to yield **5** (0.07 g) which recrystallised from pet. ether followed by sublimation *in vacuo*, m.p. 153-55°; IR: 3050, 2650, 1690, 1450, 1395, 1370, 1280, 1260, 1230, 1150, 1137, 1075, 910, 880, 850, 820 cm^{-1} PMR (CCl_4): δ 0.8 (*s*, 2H, cyclopropyl protons), 1.17 (*s*, 3H, C_1-CH_3), 1.25 (*s*, 3H, C_7-CH_3), 12.1 (*s*, 1H, carboxyl group) (Found: C, 72.3; H, 8.6. Calc. for $C_{10}H_{14}O_2$: C, 72.3; H, 8.5%).

Isolation of methyl ketosantalate (**9**)

Benzene eluates of the main chromatography which contained the methyl esters of higher acids, including **9**, on rechromatography on silica gel (1:50), followed by preparative layer chromatography and elution with benzene-ethyl acetate (6%) gave nearly pure **9**, b.p. 190-95° (bath)/1.5 mm, which was further purified via its semicabazone and regeneration.

Semicarbazone of **9**

The ester **9** (0.2 g), semicarbazide hydrochloride (0.3 g), sodium acetate (0.5 g) and methanol (5 ml) was warmed on a water-bath for 5 min and left at room temperature for 48 hr. The needle shaped crystalline material obtained was filtered washed with cold water and recrystallised from ethanol to obtaine the semicarbazone, m.p. 183-85°; IR: 3450, 3333 (NH); 1740 ($-COOCH_3$); 1690, 1590 (C=N; C=O NH $-CO-CH_2$); 1383, 1363 (*gem*-dimethyl), 1280, 1264, 1120, 1145, 1100, 1080, 1058, 940; 860, 825, 822, 3030 (tricyclene ring system); UV (ethanol): 228 nm (log ε, 4.11) (Found: C, 64; H, 8.8; N, 12.9. $C_{17}H_{27}O_3N_3$ requires C, 63.5; H, 8.5; N, 13.1%).

Regeneration of **9** *from its semicarbazone*

A solution of the semicarbazone (0.1 g) in aq acetic acid (10 ml, 70%) under CO_2 blanket was left at the room temperature for 40 hr, poured into water (150 ml), extracted with ether, the extract washed with aq Na_2CO_3 (5%), water, dried and solvent removed to yield 0.06 g of **9**, b.p. 155-56° (bath)/1 mm, $[\alpha]_D^{27}$-39° (*c*, 10.0); IR (neat): 3040, 2940, 2850, 1735 (ester), 1710 (ketone), 1455, 1430, 1405, 1365, 1345, 1170, 1140, 1080, 1040, 945; 875, 850, 820 and 750 cm^{-1}; PMR (CCl_4): 0.83 (*s*, 2H, cyclopropyl protons), 0.93 (*s*, 3H, C_1-CH_3), 1.00 (*s*, 3H, (C_1-CH_3), 1.14 (*d*, *J*=7 Hz, secondary C_{13}-CH_3), 3.65 (*s*, 3H, carbomethoxy function) and then signals in the region 2.00 to 3.00 (5H, protons on the aliphatic side chain) (Found: C, 72.6; H, 8.4. $C_{16}H_{24}O_3$ requires C, 72.7; H, 9.1%); mass: *m/z* 264 (M^+).

Preparation of ketosantalic acid (**8**) *from methyl ketosantalate* (**9**)

Methyl ketosantalate (0.1 g) and ethanolic potash (3 ml, 6%) was refluxed on a water-bath (4 hr) and worked up as in the case of teresantalic acid to afford **8** (0.7 g); b.p. 180° (bath)/0.3 mm; $[\alpha]_D^{29}$-30° (*c*, 1.4); IR: 1701, 820, 855, 877 cm^{-1} (tricyclene system) (Found: C, 72.3; H, 9.2. $C_{15}H_{22}O_3$ requires C, 72.0; H, 8.8%).

Reduction of **8** *with* $NaBH_4$: *Preparation of γ-lactone* (**10**)

To a cooled (5°) and stirred solution of **8** (0.08 g) in dioxane (2 ml, 80% aq), was added dropwise a cold solution of $NaBH_4$ (0.30 g) in dioxane (3 ml, 80% aq). Stirring was continued at the ice-bath temperature for 2 hr and then at the room temperature for 5 hr after which a fresh lot of $NaBH_4$ solution (0.04 g in 2 ml) was added at room temperature and the stirring continued overnight. From the reaction mixture dioxane was removed under reduced pressure, the residue poured into water, acidified with dil HCL, extracted with ether, the extract washed with aq Na_2CO_3 solution (5%), water, dried and the solvent removed to yield a fine crystalline solid which was further purified by preparative layer chromatography using benzene-ethyl acetate (6%), the product sublimed and crystallised twice from pet. ether to yield the γ-lactone (**10**, 15 mg), m.p. 135-36°, $[\alpha]_D^{29}$ + 3° (*c*, 1.94). The same lactone with identical properties could also be obtained by reduction of **9** with $NaBH_4$ in methanol or sodium ethanolic solution; IR (nujol): 3040, 1760 (γ-lactone), 1450, 1375, 1365, 1285, 1220, 1170, 1150, 1070, 1040, 1000, 920; 875, 850, 820 cm^{-1} (tricyclene ring system); PMR (CCl_4): δ 0.82 (*s*, 2H, cyclopropyl protons of the tricyclene ring system), 0.9 (*s*, 3H, C_1-CH_3), 1.01 (*s*, 3H, C_7-CH_3), 1.18 (*d*, *J*=6 Hz, 3H, secondary C_{13}-CH_3), 4.35 (*m*, 1H, HO) (Found: C, 76.9; H, 9.3. $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.5%).

Wolff-Kishner reduction of **9**: *Formation of nitrogencontaining compound* (**12**)

A mixture of **9** (0.1 g), hydrazine hydrate (1 ml, 100%), diethylene glycol (2 ml, freshly distilled) and KOH (0.52 g) was heated on an oil-bath at 170-80° for 7 hr under N_2 atmosphere. The cooled reaction mixture was poured into water, filtered, acidified in the cold, extracted with ether, extract washed with water, dried and the solvent removed to yield **12**, which was crystallised from pet. ether, m.p. 119-20°, $[\alpha]_D^{29}$ −16.4° (C, 3.05); IR: 3300, 3170, 1754, 16955; 870, 860, 825 cm^{-1} (tricyclene system); PMR: δ 0.82 (cyclopropyl protons), 0.88 (C_1-CH_3), 1.02 (C_7-methyl), 1.14, 1.2 (secondary methyl); other signals at 1.57, 1.7, 2.17, 2.30 (Found: C, 73.2; H, 8.9; N, 11.1. $C_{15}H_{22}N_2O$ requires C, 73.1; H, 9.0; N, 11.4%).

Semicarbazone of **9** (0.84 g) on similar reduction gave **12**, m.p. and mixed m.p. 118-19°.

Action of formic acid on **9**

A solution of **9** (0.052 g) in formic acid (1 ml) was heated on a water-bath for 7 hr and left overnight at the room temperature. The reaction mixture was poured into water, extracted with ether, extract washed with water, aq Na_2CO_3 solution (5%), water, dried and the solvent removed to give the product (0.04 g), b.p. 140-46° (bath)/0.2 mm. GLC analysis (polyester column) showed four peaks; UV: 243 nm (ε 961); IR: 2985, 1786 (-lactone), 1742 ($COOCH_3$); 1695, 1629 (α,β-unsaturated ketone), 1464, 1443; 1383, 1337 (*gem*-dimethyl); 1312, 1256, 1212, 1176, 1111, 1075, 1042, 1002, 971, 926, 893, 862, 820 (C=CH−) cm^{-1}.

No analysis was carried and no effort was made to separate the constituents.

Oxime (**34**) *of methyl ketosantalate* (**9**)

A mixture of **9** (0.25 g), ethanol (2 ml), NH_2OH, HCl

(0.3 g), AcONa (0.5 g) and aq ethanol (10 ml) was warmed on a water bath for 10 min and left at room temperature for 36 hr. The reaction mixture was diluted with water (20 ml), extracted with ether (4 × 50 ml) and the organic layer worked up in the usual way to yield the oxime which was purified by preparative layer chromatography using ethyl acetate (20%)-pet. ether to give pure **34** (180 mg); IR (thin film): 3300, 3025, 1735, 1650, 1460, 1380, 1320, 1295, 1170, 1120, 1075, 1050, 970; 875, 850, 815 cm^{-1} (Found: N, 5.2. $C_{16}H_{25}O_3N$ requires N, 5.0%).

Beckmann rearrangement of **34**: *Conversion into the amide*

(**35**): (*a*) *p-Toluenesulphonyl chloride-pyridine method*

The ester **9** (0.2 g), , *p*-toluenesulphonyl chloride (0.15 g) and pyridine (5 ml) was warmed on a water-bath for 30 min and the coloured solution left at room temperature for 48 hr. The reaction mixture was diluted with cold water (20 ml), extracted with ether (3 × 50 ml) and worked-up as usual to give a product mixture, TLC showed traces of the starting material. The pure product was obtained by preparative TLC on silica gel using chloroform (20%)-ethyl acetate as the developing solvent; IR ($CHCl_3$): 3300 (lactam grouping due to $\nu N-H$), 3040, 1735 (ester), 1640 (lactam carbonyl), 1545, 1450, 1430, 1370, 1275, 1250, 1160, 1075, 1050, 975; 875, 840, 825 (tricyclene system); 750 cm^{-1} (Found: N, 5.1. $C_{16}H_{25}NO_3$ requires N, 5.0%).

(*b*) *Dioxane-thionyl chloride method*

It was tried but found to be less satisfactory.

Acid hydrolysis of amide (**35**): *Formation of methylsuccinic acid*

The amide (**35**, 0.04 g) was heated with sulphuric acid (2 ml, 25%) on a steam-bath for 5 hr. A portion of the hydrolysate (0.5 ml) was carefully concentrated on a small flame. The concentrate was heated with a speck of resorcinal for a short time, cooled, made alkaline (KOH, 10% wt/v) when a strong reddish green fluorescence appeared indicating the presence of methylsuccinic acid.

Preparation of (−)-π-*bromotricyclene* (**20**) *from* (+)-*camphor* (**19**)

Five steps were involved. (+)-Camphor through α-bromocamphor, α,π-dibromocamphor, π-bromocamphor, hydrazone and finally oxidation with mercuric oxide gave (−)-π-bromotricyclene (**20**), b.p. 130° (bath)/18 mm, $(\alpha)_D^{28} -8.3°$ (*c*, 7.23), n_D^{24} 1.5090; IR (neat): 3049, 865, 856, 847, 820 (tricyclene ring system); 1250 cm^{-1} (C-Br); PMR: signals were consistent with the structure (Found: C, 55.60; H, 7.0; Br, 37.4. $C_{10}H_{15}Br$ requires C, 55.8; H, 7.0; Br, 37.1%).

(±)-π-*Bromotricyclene* (**20**)

Due to short supply or non-availability of optically active camphor, at some stages synthetic (±)-camphor was used to obtain (±)-**20**, b.p. 111-13°/17 mm, n_D^{30} 1.5065; IR (neat): 3040, 1450, 1430, 1368, 1305, 1280, 1270, 1240, 850, 820 cm^{-1} (Found: C, 55.6; H, 7.2; Br, 37.3. Calc for $C_{10}H_{15}Br$: C, 55.8; H, 7.0; Br, 37.1%).

Preparation of methylsuccinic anhydried (**23**)

It was prepared by adopting the multi-step reaction sequence as described in the literature, as a pale yellow viscous liquid, b.p. 240-70° (bath); IR: 3650, 2976, 2941, 1852, 1786, 1639, 1458, 1412, 1381, 1290, 1232, 1200, 1111, 1065, 1004, 926, 909, 784, 725 cm^{-1}.

Condensation of cadmium-Grignard complex of (−)-π-*bromotricyclene* (**20**) *with methylsuccinic anhydride* (**23**)

The Grignard apparatus was dried at 125°, assembled while hot, heated again with a free flame and cooled under dry nitrogen atmosphere. Dry magnesium turnings 3.3 g, dried over P_2O_5 *in vacuo*) were placed in the flask and covered with sodium-dried ether (50 ml). The mixture was stirred vigorously and treated with a crystal of iodine to initiate the reaction. (−)-π-Bromotricyclene (5.1 g in 30 ml dry ether) was added dropwise at room temperature under stirring at a fairly even rate during 45 min. The reaction mixture was refluxed by surrounding the flask with warm (40°) water heated by an IR lamp. It was cooled (ice-bath) and $CdCl_2$ (2.8 g, dry, heated at 110° for 1 hr) was added in one lot. After removing the ice-bath, the mixture was stirred for 5 min, the ether distilled off rapidly from the solution by surrounding the reaction vessel with hot water. Distillation was continued until a semisolid residue remained. To this dry, thiophene-free benzene (40 ml) was added and distillation resumed until the benzene had practically ceased to distill. To the residue was added fresh benzene (dry, 80 ml) and refluxed under stirring until the solid had dispersed through the mixture. To this was added during 15 min, a solution of methyl succinic anhydride (2.3 g) in benzene (20 ml) and the refluxing continued for 6 hr after which a very slow stream of dry nitrogen gas was passed overnight. The reaction mixture was filtered through cotton and to the filtrate cold dil sulphuric acid (150 ml, 1.5%) was added with stirring. The benzene and water layers were separated, the aqueous layer extracted 3 times with benzene and the total benzene extract washed with water, dil Na_2CO_3 solution (5% aq) water and dried. Eventually two fractions were obtained: (i) benzene fraction containing neutral material; and (ii) aqueous bicarbonate solution containing the acidic portion.

Processing of the benzene solution: *Isolation of* **30**

Removal of benzene gave the neutral product, bi-π-tricyclyl (**30**, 3.3 g), which solidified to a crystalline mass. It was crystallised two times from pet. ether, m.p. 116-17°; IR (CCl_4): 3020, 2950, 2680, 1460, 1375, 1350, 1300, 1275, 1250, 1155, 1125, 1100, 1010, 940, 875, 855 (Found: C, 88.9; H, 11.4. $C_{20}H_{30}$ requires C, 88.8; H, 11.2%).

Processing of acidic fraction: *Isolation and characterisation of* **24** *and/or* **25** *and* **28** *and/or* **27**

The sodium carbonate washings were acidified with dil hydrochloric acid, extracted with ether, washed with water, dried and the solvent removed to give the acid portion (0.33 g). This was esterified (diazomethane) to yield the ester (0.34 g), b.p. 160-75° (bath)/0.2 mm; GLC showed two peaks (TLC 2 spots). IR and PMR indicated the presence of tricyclene ring system, methylene group ($>=CH_2$), ester function and CH_2-O moiety (Found: C, 68.20; H, 8.5. $C_{16}H_{24}O_3$ requires C, 68.54; H, 8.6%).

The above ester mixture was subjected to preparative layer chromatography on silver nitrate-impregnated silica gel using ethyl acetate (6%)-benzene as the developing solvent. The two components were separated in the pure state as the fast moving and the slow moving spots.

Characterisation of 'fast moving' product (**24** *and/or* **25**)

The TLC and GLC pure fast moving compound had b.p. 150-60° (bath)/0.15 mm, $[\alpha]_D^{28}$ +4.9° (*c*, 2). IR: 3030, 853, 834, 820 (tricyclene system); 1730 (ester), 1404 (active methylene); PMR: δ 0.92 (*s*, 3H, C_1-CH_3), 1.06 (*s*, 3H, C_7-CH_3), 1.18 (*d*, *J* = 7 Hz, 3H, secondary CH_3), 3.70 (*s*, 3H, $-COOCH_3$), 3.9 (*d*, *J* = 4.5 Hz, 2H, $+CH_2-O-$) (Found: C, 68.8; H, 8.7. $C_{16}H_{24}O_4$ requires C, 68.5; H, 8.6%).

Hydrolysis of fast moving compound: *Isolation of teresantalol* (**26**)

The compound (0.025 g) was saponified with ethanolic potash (0.1 g KOH, 4 ml ethanol, boiling water-bath 3.5 hr). Ethanol was distilled off, the residue diluted with water, extracted with ether, extract washed with water, dried and solvent removed to yield **26** (0.01 g), purified by sublimation, m.p. 116°; it was found identical with an authentic teresantalol (**26**) (m.p. and mixed m.p., IR, GLC, TLC).

Characterisation of slow moving product (**28** *and/or* **27**)

The GLC and TLC pure slow moving compound had b.p. 170-75° (bath)/1.5 mm; IR: 3030, 1661, 893 ($>=CH_2$); 1730 (ester); 1626, 1460, 1431, 1376, 1364, 1339, 1266, 1205, 1163, 1052, 1000, 985, 893, 837, 750 cm^{-1}; PMR: 1.06 (3H, C_7-CH_3), 1.11, 1.25 (3H, secondary $-CH_3$), 3.6 (3H, $COOCH_3$), 3.85 (2H, CH_2-O-), 4.45, 4.76 (2H, CH_2) (Found: C, 68.8; H, 9.2. $C_{16}H_{24}O_4$ requires C, 68.5; H, 8.6%).

Hydrolysis of **28** *and/or* **27**: *Isolation of alcohol* (**29**)

Hydrolysis was carried out as in the previous case to yield **29** which was purified by sublimation, m.p. 92°; IR: 3030, 1650, 880 ($>C=CH_2$), 3340, 1040, 1027 cm^{-1} ($-CH_2OH$).

Reaction of cadmium-Grignard complex of (±)-π-*bromotricyclene* (**20**) *with the semiester acylchloride* (**22**)

Initially the Grignard reagent was prepared exactly as before using magnesium (2.1 g), ether (50 ml), (±)-π-bromotricyclene (2.2 g) in ether (30 ml). After preparation was complete, cadmium chloride (1.1 g) was added to it in one lot under N_2 atmosphere. Further processing was done as before. A solution of the acid chloride (1.3 g) in benzene (25 ml) was added during 15 min and refluxing continued for 2 hr, after which a stream of nitrogen was maintained overnight. Further processing eventually yielded as the main product (2.2 g) a neutral material in benzene which, as before, proved to be bi-π-bromotricyclyl (**30**), m.p. 112-14°, gave correct elemental analyses and identical infrared spectrum.

The minor component, the acidic portion, after esterification (diazomethane) proved to be identical with the fast moving compound of the earlier reaction, b.p. 158-62° (bath)/0.2 mm; IR (neat): 3040, 2930, 1735, 1460, 1430, 1405, 1375, 1340, 1310, 1275, 1225, 1160, 1070, 1055, 995; 880, 850, 830, 820 cm^{-1}; PMR (CCl_4): δ 0.9 (*s*, 3H), 1.05 (*s*, 3H), 1.19 (*d*, *J* = 7 Hz, 3H), 3.63 (*s*, 3H), 3.89 (*d*, *J* = 4 Hz, 2H) (Found: C, 68.8; H, 8.7. $C_{16}H_{24}O_4$ requires C, 68.5; H, 8.6%). Hydrolysis, as before, yielded Teresantalol (**26**), purified by crystallisation from pet. ether and sublimation, m.p. 114°, superimposable IR spectrum with authentic sample (Found: C, 78.5; H, 10.9. $C_{10}H_{16}O$ requires C, 79.0; H, 10.5%).

Isolation of pure α-*santalyl acetate* (**37**)

The neutral fraction of sandalwood oil obtained after removal of the acids via saponification was distilled under reduced pressure and the fraction b.p. 120-25°/0.5 mm collected. It was acetylated at the room temperature using pyridine and acetic anhydride. The crude acetate was distilled *in vacuo* to yield a mixture of α- and β-santalyl acetates, b.p. 151-53°/6 mm. The mixture (20.0 g) was poured onto a column of silver nitrate-impregnated silica gel (800 g). The column was eluted with sodium-dried pet. ether (60-80°). After removal of the small amount of hydrocarbon fraction (monitored by GLC/TLC), α-santalyl acetate was eluted with the same solvent.

When most of it was removed, the solvent polarity was changed to pet. ether-ethyl acetate (95:5) and most of the β-santalyl acetate was eluted out. The α-santalyl acetate fractions showing purity over 95% (GLC) were collected separately, concentrated and distilled (9.2 g), b.p. 122-24° (bath)/0.2 mm; IR: 3040, 2950, 2860, 1740, 1405, 1370, 1230, 1160, 1155, 1140, 1080, 1030, 875, 845, 820 cm^{-1} PMR: 0.83 (*s*, 5H), 1.05 (*s*, 3H), 1.71 (*s*, 3H), 1.96 (*s*, 3H), 4.51 (*s*, 2H), 5.33 (*m*, 1H) (Found: C, 77.6; H, 9.8. Calc. for $C_{17}H_{26}O_2$; C, 77.8; H, 9.9%).

t-Butylchromate oxidation of α-santalyl acetate: Isolation of the nor-acetate (**40**)

The reagent was prepared by the addition of anhydrous chromium trioxide (16.0 g) to a cooled mixture of carbon tetrachloride (250 ml) and *t*-butanol (40 ml). It was stirred at the room temperature for 2 hr and then left overnight after addition of anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure (150 ml). To this mixture, acetic anhydride (30 ml) and acetic acid (15 ml) were added. Subsequently, to a stirred solution of α-santalyl acetate (6.0 g) in CCl_4 (50 ml), the above reagent was added dropwise during 30 min. The reaction mixture was stirred and refluxed for 36 hr, cooled, treated with an aqueous solution of oxalic acid (30 g, 100 ml) and stirred at the room temperature for 3 hr. The organic layer was separated and the aqueous layer extracted with ether (3 × 150 ml). The combined organic layer was washed with saturated bicarbonate solution, brine, dried (Na_2SO_4) and the solvent removed to yield the reaction product (5.7 g). GLC/TLC showed the presence of considerable about of starting material, besides one major and three minor products. The product mixture was chromatographed on silica gel (210.0 g) and eluted with pet. ether when most of the starting material was eluted out. Pet. ether-ethylacetate (90:10) eluted the main product. The fractions showing purity over 95% (GLC), were collected, combined and distilled under reduced pressure, b.p. 125-27° (bath)/0.4 mm (1.82 g); IR (neat): 3050, 2950, 2875, 1740 (acetate), 1720 ($\geq$ =O), 1450, 1425, 1370, 1280, 1240, 1150, 1125, 1070, 1025, 880, 850, 820 cm^{-1} (tricyclene system), UV: no absorption in the region 220-244 nm; PMR (CCl_4): 0.83 (*s*, 5H), 1.03 (*s*, 3H), 2.06, 2.1 (6H), 4.85 (*t*, 1H) (Found: C, 72.5; H, 9.3. $C_{16}H_{24}O_3$ requires C, 72.7; H, 9.1%); Mass: *m/z* 264 (M^+).

Bis-2,4-DNP derivative of the nor-acetate (**41**)

The derivative was prepared following the standard procedures and was crystallised from ethanol, m.p. 215-17°; UV (λ_{max} nm, log ε): 255 (4.2), 394 (4.49), 440 (4.4) (Found: N, 18.8. $C_{26}H_{28}N_8O_8$ requires N, 19.3%).

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Synthesis of (±) Ethyl (*E*)-7-Acetoxy-4-oxo-2-octenoate: The Key Synthon of Pyrenophorin†

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Starting from furan, which serves as a masked 3-acyl acrylate, (±) ethyl (*E*)-7-acetoxy-4-oxo-2-octenoate (**3**) has been synthesized.

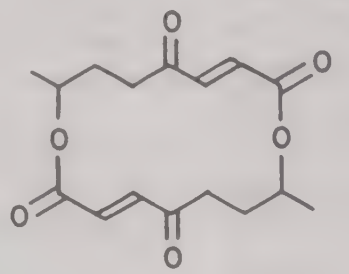
Pyrenophorin (**1**), a macrolide isolated from the culture filtrates of *Pyrenophora avenae* and *Stemphylium radicinum* is one of the most extensively studied macrolides[1]. Most of the studies on **1** have been directed to the synthesis of the C_8-monomer unit (**2**) followed by the classical Mitsunobu reaction involving diethyl azodicarboxylate and triphenylphosphine to form the dimer (**1**) (Scheme 1).

The synthesis of **2** would involve synthesis of the 3-acyl acrylate moiety as is present in **1**. We envisaged to synthesize **2** using a appropriately substituted furan derivative, since furans are known to act as masked acyl acrylate synthons[2]. A recent report by Rosini *et al.*[3] prompts us to disclose our own results in this direction.

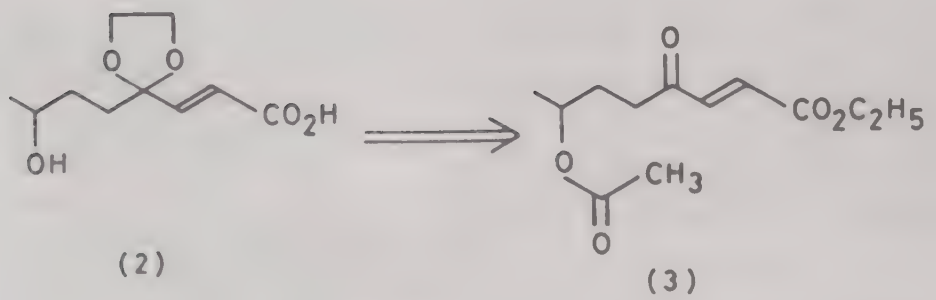
Our strategy for the synthesis of (±)ethyl(*E*)-7-acetoxy-4-oxo-2-octenoate (**3**) which forms the precursor for **2** is summarized in Scheme 2.

(±)-4-(2-Furyl)-butan-2-ol (**5**) was obtained in 80% yield by the alkylation of furan with 1-iodo-3-hydroxybutane[4] (**4**) in presence of *n*-BuLi in THF. The OH group of **5** was protected as its acetate using standard conditions to give **6** in quantitative yield.

Though the opening of the furan ring to provide substituted 3-acyl acylate moiety has been well documented, we were particularly attracted by the methodology developed by Jurczak *et al.*[2], because of the mildness of the reaction conditions and the high yields of the reaction. Accordingly, when **6** was treated with $Br_2/Py/H_2O$/acetone at −20°C followed by stirring of the reaction mixture at room temperature overnight, substituted ene-dione (**7**) was obtained in 85% yield. Oxidation of **7** under mild conditions using $NaClO_2/NaH_2PO_4$ and 2-methyl-2-butene led to the acid (**8**) in 75% yield. Compound (**8**) on treatment with ethyl bromide and DBU using acetonitrile as the



(1)



(2) (3)

Scheme 1

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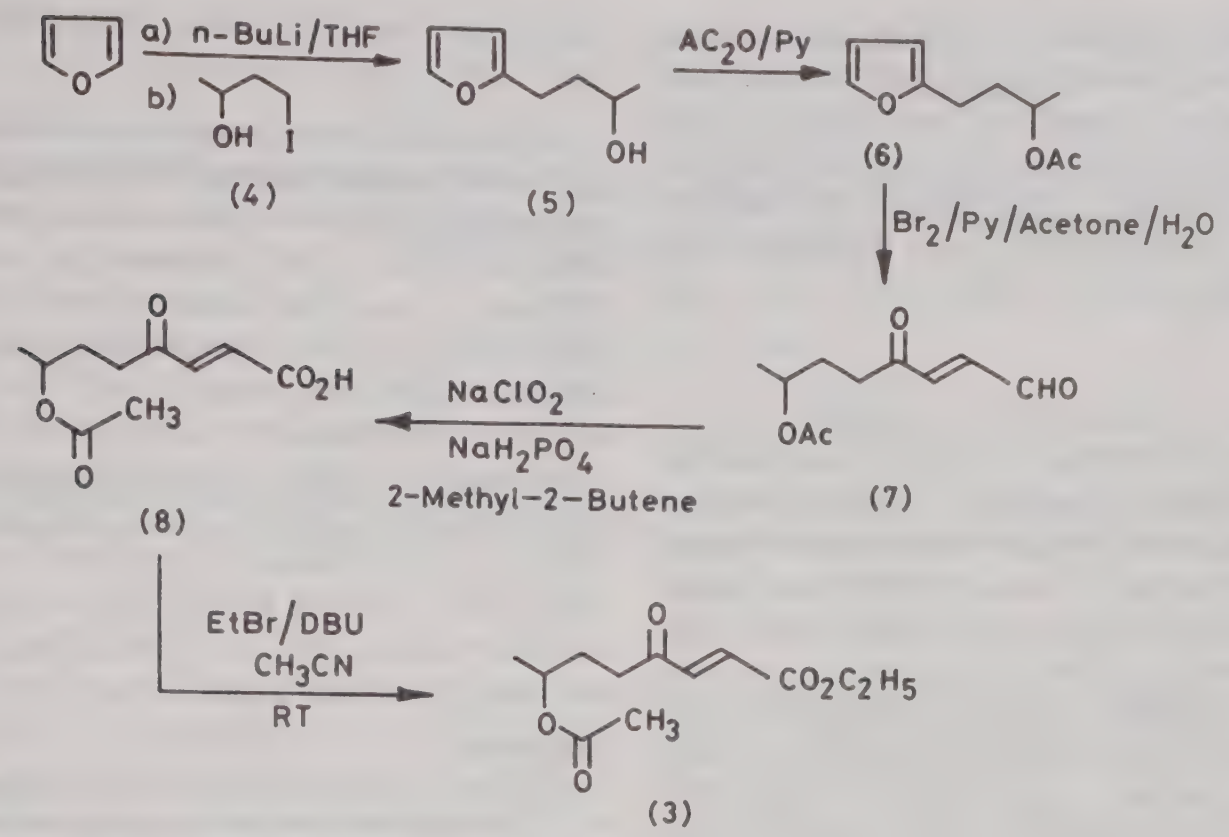

Scheme 2

solvent at room temperature for 4 hr gave the title compound (**3**) in 70% yield. Since ketalization and saponification of **3** to give **2** and the dimerization of **2** to **1** has already been achieved[5], our route constitutes a formal total synthesis of pyrenophorin (**1**).

The easy availability of the starting materials, mildness of the reaction conditions used throughout the reaction sequences and the high yields obtained in all the steps, are significant features of our synthetic route to pyrenophorin.

Experimental Procedure

All PMR spectra were recorded on a Varian FT-80 NMR spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard; chemical shifts are expressed in δ-scale. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer-683 IR spectrophotometer. Melting point was recorded on a kofler hot plate.

(±)-4-(2-*Furyl*)-*butan*-2-*ol* (**5**)

In a flame-dried and evacuated 100 ml two-necked RB flask under N_2 atmosphere was added furan (1 ml, approximately 2 eq) dissolved in THF (10 ml). The flask was cooled to −40°C, *n*-BuLi (5 ml) was added gradually via a syringe to generate the anion and the contents were stirred at −40°C for 4 hr. To this was added a dry THF (10 ml) solution of 1-iodo-3-hydroxybutane (1 g; 5 m mol) dropwise and the reaction allowed to continue for a further 1 hr at −40°C and at room temperature for 12 hr.

The reaction was quenched by adding saturated aq NH_4Cl. The reaction mixture was extracted with ethyl acetate (25 ml), organic extract washed with water (2 × 25 ml), dried (Na_2SO_4) and concentrated to yield a syrupy compound, yield 0.87 g (80%) (Found: C, 68.6; H, 8.5. $C_8H_{12}O_2$ requires C, 68.6; H, 8.6%); IR (neat): 3360 (O−H); PMR: 7.32-7.15 (*m*, 1H) 6.3-6.15 (*m*, 1H) 6-5.85 (*m*, 1H) 4-3.6 (*m*, 1H), 2.8-2.6 (*t*, 2H), 1.75-1.6 (*m*, 3H), 1.9 (*s*, 1H, disappeared on treatment with D_2O), 1.2 (*d*, 3H, J=6.3 Hz).

(±)-4-(2-*Furyl*)-*butan*-2-*ol acetate* (**6**)

To the alcohol (**5**) (500 mg; 3.5 mmol) dissolved in dry pyridine (0.6 ml, 2 eq) and taken in a 25 ml RB flask with a guard tube was added dropwise acetic anhydride (0.4 ml, 1.1 eq) with exclusion of moisture and stirred for 2 hr at room temperature. The reaction mixture was extracted with ether (25 ml), washed with water (2 × 25 ml), 2*N* HCl (2 × 10 ml), water (2 × 25 ml), saturated aq $NaHCO_3$ (2 × 25 ml), water (2 × 25 ml), dried (Na_2SO_4) and concentrated to yield a syrupy compound, yield 0.52 g (90%) (Found: C, 66.2; H, 7.9. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.7%); IR(neat): 1740 (C=O); PMR: 7.3-7.2 (*m*, 1H), 6.25-6.15 (*m*, 1H), 5.95-5.85 (*m*, 1H), 5-4.75 (*m*, 1H), 2.65-2.55 (*t*, 2H), 2.0 (*s*, 3H), 1.9-1.7 (*m*, 3H), 1.25 (*d*, 3H, J=6.3 Hz).

(±)-(*E*)-7-*Acetoxy*-4-*oxo*-2-*octenal* (**7**)

To a solution of **6** (500 mg; 2.74 mmol) and pyridine (0.894 ml) in acetone-water (85:15, v/v, 27 ml), vigorously stirred and cooled to −20°C was added dropwise Br_2 (0.141 ml) in acetone-H_2O (4:1 v/v, 5 ml). After the addition of bromine the reaction mixture was allowed to attain room temperature and then stirred for 12 hr. The reaction mixture was taken into ether

(25 ml), washed with brine (2 × 25 ml), saturated aq $CuSO_4$ (2 × 25 ml), dried (Na_2SO_4) and concentrated to yield a syrupy compound, yield 0.462 g (85%) (Found: C, 60.5; H, 7.2. $C_{10}H_{14}O_4$ requires C, 60.6; H, 7.1%); IR(neat): 1690 (C=O) 1730 (C=O); PMR: 9.8 (*d*, 1H), 6.85-6.75 (*m*, 2H), 5.05-4.8 (*m*, 1H), 2.85-2.65 (*t*, 3H), 2.05 (*s*, 3H), 2-1.85 (*m*, 2H), 1.26 (*d*, 3H, *J* = 6.3 Hz).

(±)-(*E*)-7-*Acetoxy*-4-*oxo*-2-*octenoic acid* (**8**)

The aldehyde (**7**) (300 mg; 1.51 mmol) was dissolved in *t*-BuOH (25 ml) containing 2-methyl-2-butene (10 ml). A solution of sodium chlorite and sodium dihydrogen phosphate in water (10 ml) was added dropwise to the above solution at 10 min interval. The pale yellow reaction mixture was stirred at room temperature overnight, volatile compounds were removed *in vacuo*, the residue was dissolved in water (30 ml) and extracted with CH_2Cl_2 (10 ml). The aqueous layer was acidified to *p*H3 with HCl and extracted with chloroform (3 × 20 ml). The combined chloroform layer was washed with cold water (50 ml), dried (Na_2SO_4) and concentrated to yield a solid, yield 0.243 g (75%), m.p. 66°C (lit[6] m.p. 66-66.5°) (Found: C, 56.1; H, 6.6. $C_{10}H_{14}O_5$ requires C, 56.1; H, 6.6%); IR($CHCl_3$): 3600-2800 (CO_2H), 1740-1700 (C=O br); PMR: 7.48 (*s*, 1H, disappeared on treatment with D_2O), 7.08 (*d*, 1H, *J* = 16 Hz), 6.7 (*d*, 1H, *J* = 16 Hz), 4.8-5.1 (*m*, 1H), 2.75 (*t*, 2H), 2.01 (*s*, 3H), 1.9-2.0 (*m*, 2H), 1.28 (*d*, 2H, *J* = 6.3 Hz).

(±)-*Ethyl*-(*E*)-7-*acetoxy*-4-*oxo*-2-*octenoate* (**3**)

To a well-stirred solution of **8** (60 mg, 0.28 mmol) in acetonitrile (5 ml) was added with the help of a syringe DBU (0.04 ml, 1 eq) followed by ethyl bromide (0.03 ml, 1.5 eq). The contents were stirred at room temperature for 6 hr, diluted with water (20 ml) and extracted twice with ether (25 ml). The ether extract was washed with water (2 × 20 ml), dried (Na_2SO_4) and concentrated to yield a syrupy compound, yield 47 mg (70%) (Found: C, 59.3; H, 7.2. $C_{12}H_{18}O_5$ requires C, 59.5; H, 7.4%); IR(neat): 1720-1760 (C=O br); PMR: 7.1 (*d*, 1H, *J* = 16 Hz), 6.75 (*d*, 1H, *J* = 16 Hz), 4.8-5.15 (*m*, 1H), 4.25 (*q*, 2H), 2.65 (*t*, 2H), 2.01 (*s*, 3H), 1.9-2.0 (*m*, 2H), 1.52-1.08 (*m*, 6H).

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Synthesis of 3-Acetamido- & 3-Azido-3-deoxy-1,2-O-isopropylidene-α-D-xylohexofuran-5-ulose*

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The 3-substituted-5,6-ene derivatives (**10** and **14**), prepared from diacetoneglucose, have been subjected to oxymercuration-demercuration reaction. The resulting 5-hydroxy compounds (**11** and **16**) have been oxidised to the title compounds (**12** and **17**).

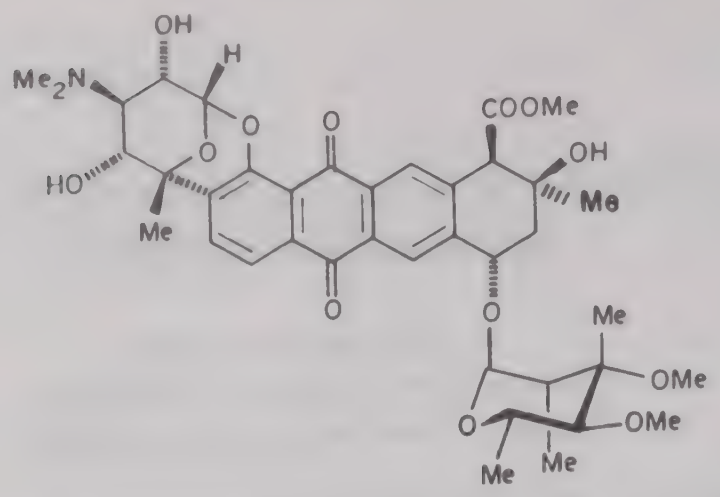
As a part of a programme on the chiral synthesis of C-glycoside segment of nogalamycin[1], we required 3-acetamido- and 3-azido-5-uloses of the type **1**. Derivatives of 5-uloses have been recognised[2,3] as versatile intermediates in natural products chemistry for the formation of C−C bond. Normally these compounds in sugar series are prepared either by periodate oxidation of the 5,6-diol (**2**) followed by reaction with methylmagnesium iodide and oxidation, or by reduction of 5,6-epoxide (**3**) or the 6-tosylate (**4**) with lithium aluminium hydride (LAH) followed by oxidation of the resulting 5-alcohol (**5**)[4] (Scheme 1). However, in the first method one carbon is lost during periodate oxidation and consequently added via the Grignard reaction. In addition to this, the intermediary aldehyde (**6**), in a few cases, is likely to be unstable and therefore may lead to isomerization and lowering of yield of the final product. The second route, however, could not be employed in the present case because of the presence of acetamido and azide groups which are prone to LAH reduction. Moreover, this route involves selective protection-deprotection reactions. We now report a convenient procedure for 5-uloses which to some extent circumvent these problems.

Earlier report from these laboratories[5] has indicated that 3-azido-3-deoxy-1,2,5,6-di-O-isopropylidene-α-D-glucofuranose (**7**) can be prepared in two high yielding steps starting from diacetone-glucose. Reduction of the azido group in **7** followed by acetylation gave rise to the known[6] 3-acetamido-derivative (**8**). Selective removal of the 5,6-isopropylidene group in **8** in the presence of dilute acid followed by O-mesylation furnished the dimesylate (**9**)[7], which on treatment with sodium iodide in refluxing ethyl methyl ketone gave the 5,6-ene derivative (**10**) in 79% yield. The PMR spectrum of **10** was in agreement with the assigned structure. All the protons were unambiguously assigned by proton decoupling experiments.

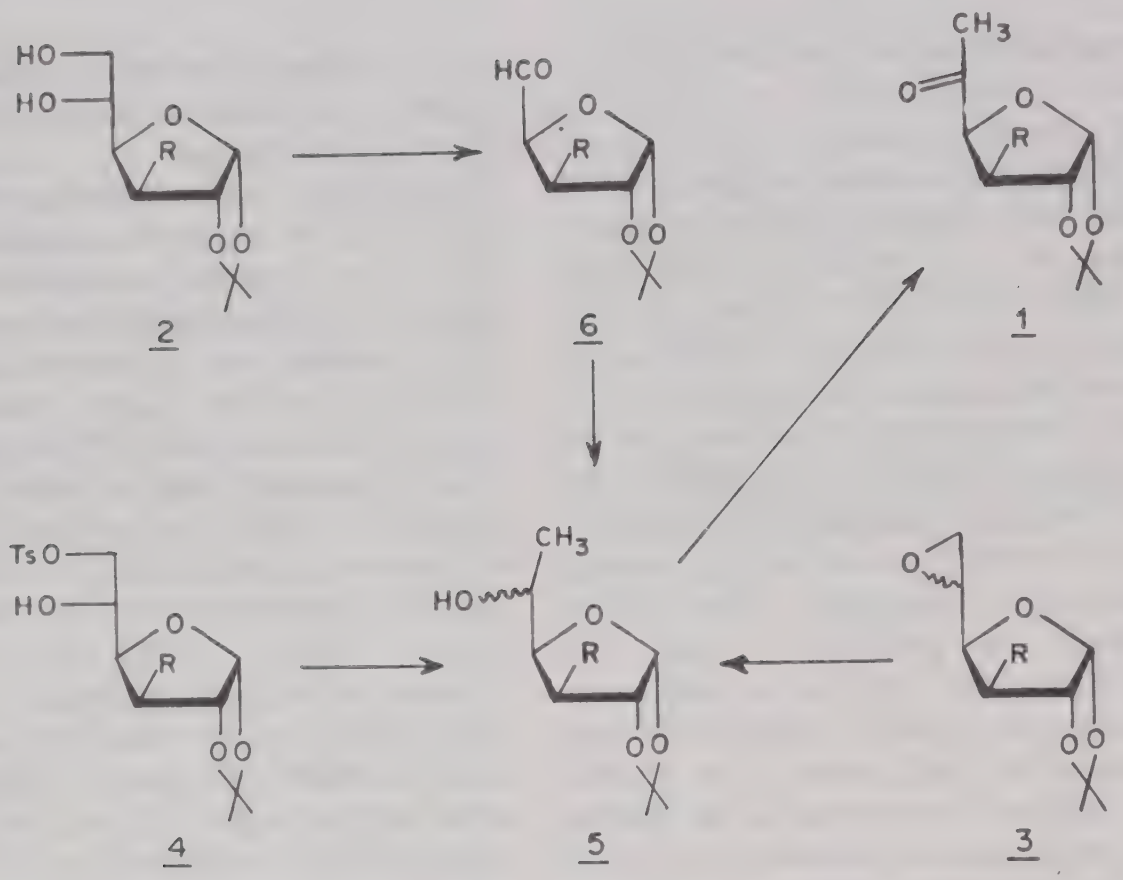
Oxymercuration-demercuration reaction[8] of **10** was carried out by successive treatment with mercuric acetate and sodium borohydride under alkaline conditions to afford a major and a minor product. The minor product was discarded while the major component isolated in 65% yield, was assigned structure (**11**) on the basis of PMR spectrum. Although **11** was isomerically pure as judged by TLC and GC analysis, no efforts were made to determine the absolute stereochemistry at C-5, in view of the fact that chirality at this centre was likely to be destroyed in next reaction. Oxidation of **11** with pyridinium chlorochromate in methylene chloride at room temperature yielded the required 5-ulose derivative (**12**) in 81% yield. The PMR spectrum of **12** displayed four singlets in the highfield region of 1.2-2 ppm corresponding to methyl groups of isopropylidene, N-acetyl and H-6,6′ and 6″. In addition, two doublets due to H-1 and H-2 and a multiplet due to H-3 and H-4 were also located.

For the synthesis of 3-azido-5-ulose derivative (**17**), the compound (**7**) was chosen and subsequently converted into the 5,6-ene derivative (**14**) by the reported procedure[5] which involved hydrolysis of 5,6-isopropylidene group, mesylation (to **13**) and treatment with sodium iodide. When the PMR spectrum of **14** was compared with that of **10**, it revealed that except for signals due to H-3 which showed an upfield shift of 0.98 ppm, all other ring protons had comparable chemical shifts. Oxymercuration-demercuration reaction of **14**, carried out as above in the case of **10** afforded two products after chromatography in almost equal amounts. The first to be isolated in 41% yield, was the required 6-deoxy derivative (**15**). The doublet due to H-6,6′,6″ in PMR spectrum of **15** clearly supported the assigned structure. The slower moving product was

* NCL Communication No. 4027.



NOGALAMYCIN



SCHEME 1

assigned the structure (**16**), because of the fact that its PMR spectrum revealed a multiplet for H-5,5′ around δ 2.0 and a triplet for H-6,6′ at 3.75 whereas other protons resonated at the expected chemical shifts.

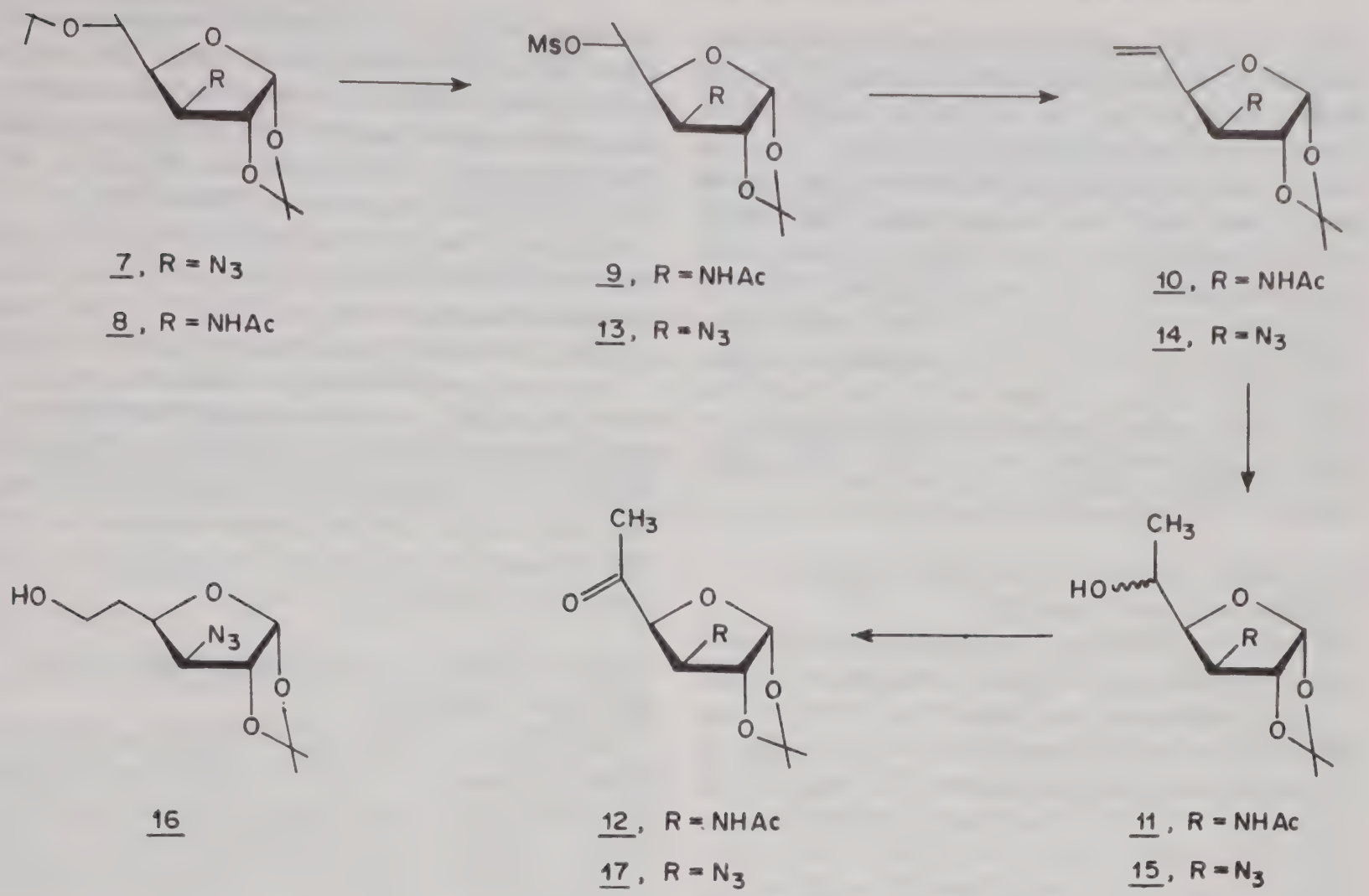
Compound (**15**) was oxidised in the presence of pyridinium chlorochromate to give the **5**-ulose (**17**) in 98% yield. In the PMR spectrum of **17**, signals due to isopropylidene methyls and C-5 methyl were located between 1.5 and 2.5 ppm while H-1, H-2, H-3 and H-4 appeared between 4 and 6 ppm.

From the above results, it is reasonable to point out that the methodology reported herein for 5-uloses is convenient than the normal methods of its formation because: (i) no carbon atom is lost or added; (ii) selective protection-deprotection is avoided; and (iii) reaction conditions are mild and easy to operate.

Experimental Procedure

3-Azido-3-deoxy-(1,2:5,6)*-di-O-isopropylidene-α-*D*-glucofuranose* (**7**)

A mixture of 3-iodo-3-deoxy-(1, 2:5, 6)-di-*O*-isopropylidene-α-D-allofuranose[9] (5.0 g, 13.5 mmol) in dimethylformamide (25 ml) containing sodium azide (10.0 g, 153.8 mmol) was heated at 110° for 48 hr. The mixture was cooled, diluted with water and extracted



with ether. The ethereal layer was washed with water, dried and concentrated. Purification on a column of silica gel using ethyl acetate-light petroleum (1:10) as eluent afforded **7** (3.1 g, 91%) as a syrup, $[\alpha]_D$ $-36.5°$ (*c*, 0.87, chloroform) (lit.[6] $[\alpha]_D-36°$ (chloroform).

3-*Acetamido*-3-*deoxy*-(1,2:5,6)-*di*-*O*-*isopropylidene*-α-D-*glucofuranose* (**8**)

The compound (**7**, 3.1 g, 10.87 mmol) in methanol (30 ml) was hydrogenated over 10% Pd/C (0.4 g) at normal pressure and temperature for 18 hr. The catalyst was filtered through celite, concentrated and the residue treated with acetic anhydride (4 ml) and pyridine (20 ml) for 4 hr. Usual work-up afforded a product which crystallised from chloroform-light petroleum to afford **8** (2.65 g, 81%), m.p. 98° (lit.[6] 95-96°); $[\alpha]_D-39.7°$ (*c*, 0.7, chloroform) (lit.[6] $[\alpha]_D-39.7°$ (chloroform).

3-*Acetamido*-3-*deoxy*-1,2-*O*-*isopropylidene*-5,6-*di*-*O*-*mesyl*-α-D-*glucofuranose* (**9**)

A solution of **8** (2.65 g, 8.8 mmol) in methanol (25 ml) containing 0.8% aq. sulphuric acid (12 ml) was stirred at room temperature overnight. The solution was neutralised with solid barium carbonate, filtered and co-distilled with benzene. The residue was treated with pyridine (12 ml) and mesyl chloride (4 ml) initially at 0° and then at room temperature for 2.5 hr. After usual work-up, the product was chromatographed over silica gel using ethyl acetate-methanol (9:1) as eluent to afford **9** (2.7 g, 73%), m.p. 120°; $[\alpha]_D+4.9°$ (*c*, 2, chloroform) (lit.[7] m.p. 124-25°; $[\alpha]_D+5°$ (chloroform).

3-*Acetamido*-3,5,6-*trideoxy*-1,2-*O*-*isopropylidene*-α-D-*xylohexofuran*-5-*ene* (**10**)

A mixture of **9** (2.7 g, 6.47 mmol) in dry ethyl methyl ketone (75 ml) and sodium iodide (4 g) was heated under reflux for 6 hr. The solvent was removed under diminished pressure, and the residue partitioned between water and chloroform. The chloroform layer was successively washed with aq sodium thiosulphate, aq sodium carbonate, water, dried and concentrated. The resulting product was purified by column chromatography over silica gel using ethyl acetate as solvent to afford **10** (1.15 g, 79%), $[\alpha]^D-29°$ (*c*, 0.9, chloroform); PMR ($CDCl^3$): δ 1.2[8], 1.50 (2*s*, 6H, CMe_2), 1.93 (*s*, 3H, NAc), 4.28 (*m*, 1H, H-4), 4.54 (*d*, 1H, H-2), 4.78 (*m*, 2H, H-1, H-5); mass spectrum: *m/z* 212 (M^+-15) (Found: C, 57.9; H, 7.7; N, 6.2. $C_{11}H_{17}NO_4$ requires C, 58.1; H, 7.5; N, 6.2%).

3-*Acetamido*-3,6-*dideoxy*-1,2-*O*-*isopropylidene*-α-(*gluco*/*iodo*)-*furanose* (**11**)

To compound (**10**, 1 g, 4.4 mmol) in a 1:1 tetrahydrofuran-water mixture (28 ml) was added mercuric acetate (1.4 g, 4.4 mmol) with stirring. After

1.5 hr, 1*M* aq sodium hydroxide (8 ml) was introduced followed by sodium borohydride solution (0.08 g of $NaBH_4$ dissolved in 6 ml of 1*M* aq NaOH). After stirring at ambient temperature for another 1.5 hr, the mixture was extracted with chloroform, the organic extract was dried and concentrated. The residue was chromatographed over silica gel with ethyl acetate-methanol (9:1) as eluent to afford **11** (0.7 g, 65%); PMR ($CDCl_3$): δ 1.31, 1.37, 1.53 (*t*, 9H, CMe_2 + Me), 1.98 (*s*, 3H, NAc), 2.6 (*bs*, 1H, OH), 3.6-4.2 (*m*, 2H, H-3, 5), 4.33 (*m*, 1H, H-4), 4.57 (*d*, 1H, H-2), 5.84 (*d*, 1H, H-1), 7.2 (*d*, 1H, NH); IR (liquid): 3400 cm^{-1} (OH) (Found: C, 54.1; H, 7.8; N, 5.6. $C_{11}H_{19}NO_5$ requires C, 53.8, H, 7.75; N, 5.7%).

3-*Acetamido*-3,6-*dideoxy*-1,2-*O*-*isopropylidene*-α-D-*xylohexofuran*-5-*ulose* (**12**)

A solution of **11** (0.5 g, 2.04 mmol) and pyridinium chlorochromate (1 g, 4.6 mmol' in methylene chloride at room temperature was stirred for 36 hr. It was diluted with ether and transferred over dry silica gel column. Elution with ethyl acetate afforded **12** (0.4 g, 81%), $[\alpha]_D - 32°$ (*c*, 0.3, chloroform); PMR ($CDCl_3$): δ 1.28, 1.50 (2*s*, 6H, CMe_2), 1.90 (*s*, 3H, NAc), 2.15 (*s*, 3H, $COCH_3$), 4.53 (*d*, 1H, H-2), 4.85 (*m*, 2H, H-3,4), 5.93 (*d*, 1H, H-1), 6.37 (*d*, 1H, NH); mass spectrum: *m/z* 243 (M^+), 228 ($M^+ - 15$) (Found: C, 54.6; H, 7.2; N, 5.5. $C_{11}H_{17}NO_5$ requires C, 54.3; H, 7.0; N, 5.7%).

3-*Azido*-3,5,6-*trideoxy*,1,2-*O*-*isopropylidene*-α-D-*xylohexofuran*-5-*ene* (**14**)

The known 3-azido-3-deoxy-5,6-di-*O*-mesyl-1,2-*O*-isopropylidene-α-D-glucofuranose[9] (6.2 g, 15.46 mmol) in ethyl methyl ketone (150 ml) containing sodium iodide (9.27 g) was heated under reflux for 8 hr. The reaction mixture was concentrated, partitioned between water and chloroform, the chloroform layer washed with aq sodium thiosulphate, aq sodium hydrogencarbonate, water, dried and concentrated. The residue obtained was chromatographed on a column of silica gel using ethyl acetate-light petroleum (1:10) to afford **14** (3.06 g, 94%), $[\alpha]_D - 44°$ (*c*, 0.7, chloroform); PMR ($CDCl_3$): δ 1.32, 1.50 (2*s*, 6H, CMe_2), 3.80 (*d*, 1H, H-3), 4.56 (*m*, 2H, H-2,4), 5.2-5.5 (*m*, 2H, H-6,6'), 5.7-6.1 (*m*, 2H, H-1,5); mass spectrum: *m/z* 196 ($M^+ - 15$) (Found: C, 51.3; H, 6.4; N, 19.7. $C_9H_{13}N_3O_3$ requires C, 51.1; H, 6.1; N, 19.9%).

Oxymercuration-demercuration reaction of **14**.

To a stirred solution of **14** (3 g, 14.2 mmol) in a 1:1 mixture of tetrahydrofuran-water (40 ml) was added mercuric acetate (4.5 g, 14.2 mmol). After 1.5 hr at room temperature, 3*M* aq. sodium hydroxide (30 ml) was added followed by alkaline solution of sodium borohydride (0.15 g, dissolved in 15 ml of 3*M* NaOH solution). After 1.5 hr, the solution was extracted with chloroform, dried and concentrated. The resulting mixture was subjected to column chromatography on silica gel using ethyl acetate-light petroleum as eluent. The first product to be eluted was **15** (1.32 g, 41%), $[\alpha]_D - 37°$ (*c*, 0.7, chloroform); PMR ($CDCl_3$): δ 1.29, 1.48 (2*s*, 6H, CMe_2), 1.31 (*d*, 3H, H-6,6',6''), 2.0 (*bs*, 1H, OH), 4.0 (*m*, 3H, H-3,4,5), 4.57 (*d*, 1H, H-2), 5.81 (*d*, 1H, H-1); mass spectrum: *m/z* 214 ($M^+ - 15$) (Found: C, 47.5; H, 6.9. $C_9H_{15}N_3O_4$ requires C, 47.2; H, 6.55%).

The second product from the column was **16** (1.32 g, 41%), $[\alpha]_D - 25°$ (*c*, 0.6, chloroform); PMR ($CDCl_3$): δ 1.28, 1.50 (2*s*, 6H, CMe_2), 1.6 (*bs*, 1H, OH), 1.8 (*m*, 2H, H-5,5'), 3.75 (*t*, 3H, H-6,6') 4.31 (*m*, 1H, H-4), 4.59 (*d*, 1H, H-2), 5.81 (*d*, 1H, H-1); mass spectrum: *m/z* 229 (M^+) (Found: C, 47.3; H, 6.7; N, 18.2. $C_9H_{15}N_3O_4$ requires C, 47.2; H, 6.5; N, 18.3%).

3-*Azido*-3,6-*dideoxy*-1,2-*O*-*isopropylidene*-α D-*xylo*-*hexofuran*-5-*ulose* (**17**)

The mixture of **15** (0.9 g, 3.9 mmol) and pyridium chlorochromate (2.5 g, 11.6 mmol) in methylene chlorides stirred at room temperature overnight. It was diluted with ether and transferred over dry silica gel column. Elution with ethyl acetate-light petroleum (1:1) afforded **17** (0.88 g, 98%), $[\alpha]_D - 107°$ (*c*, 0.6, chloroform); PMR ($CDCl_3$): δ 1.31, 1.47 (2*s*, 6H, CMe_2), 2.25 (*s*, 3H, $COCH_3$), 4.23 (*d*, 1H, H-3), 4.60 (*m*, 2H, H-2,4), 5.96 (*d*, 1H, H-1): mass spectrum: *m/z* 184 (M − 43), 159 (M − 58); GC analysis on ov 101 column: single peak, RT 1.67, column temperature 200° (Found: C, 47.2; H, 5.8, N, 18.7. $C_9H_{13}N_3O_4$ requires C, 47.5; H, 5.7; N, 18.5%).

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Synthesis of Kielcorin†

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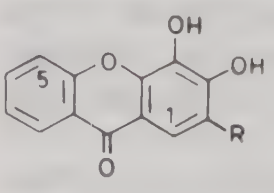
The synthesis of kielcorin, 2,3-dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethyl-5-methoxy-7*H*-1,4-dioxino[2,3-*c*]xanthen-7-one (**13**) and desemethoxykielcorin (**12**), a model compound have been accomplished. The intermediate ethyl O-benzylvanilloyl bromoacetate (**5**) serves as one-half of the molecular framework of **13** and **12**, the other halves being 3-benzyloxy-4-hydroxy-2-methoxyxanthone (**4**) and 3-benzyloxy-4-hydroxyxanthone (**3**) respectively.

In the chronology of natural products, the xanthonolignoids have entered quite recently. Although first compound of this series, kielcorin was isolated in 1969 from *Kielmeyara*[1] species (Guttiferae), the partial structure (**13**) (without regiospecific attachment of hydroxymethyl and substituted aryl groups) was assigned[2] to it only in 1977. The complete structure and stereochemistry of 1,4-dioxane ring[3] in kielcorin were established in 1978 and it was found to be an enantiomeric mixture of 2,3-dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethyl-5-methoxy-7*H*-1,4-dioxino[2,3-*c*]xanthen-7-one (**13**). The stereochemistry of 1,4-dioxane bridge was determined as *trans*-diaxial by NMR spectroscopy. The regiospecific orientation of 4-hydroxy-3-methoxyphenyl and hydroxymethyl groups was determined by alkaline hydrolysis of dioxane ring at 3-position of xanthone nucleus[3], but no unambiguous evidence was provided for the proposed structure (**13**).

A search in literature revealed that the synthesis of kielcorin has not been reported so far. Further in our work on the ethyl acetate soluble fraction of *Hypericum mysorense* Heyne we obtained hypericorin along with kielcorin[4]. This fraction also possessed antifungal activity against *Trichophyton mentegrophytes*. Keeping this in view and the availability of authentic material, we became interested in the synthesis of **13**. Before attempting this we undertook synthesis of a model compound, viz. desmethoxykielcorin (**12**) lacking one methoxyl group in xanthone part of the molecule.

For the synthesis of **12**, the key intermediate, 3-benzyloxy-4-hydroxyxanthone (**3**) was prepared by selective benzylation of 3,4-dihydroxyxanthone (**1**) which in turn was prepared from salicylic acid and pyrogallol[5]. The intermediate ethyl O-benzylvanilloyl bromoacetate (**5**) was prepared in six steps starting from vanillin employing known procedure[6,7]. The two



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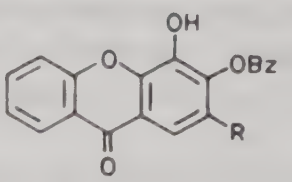

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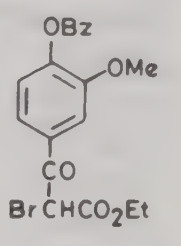

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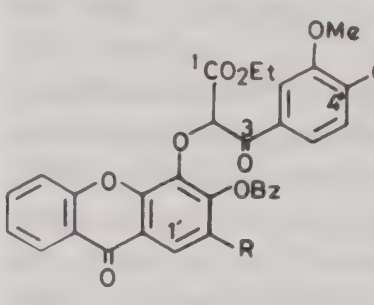

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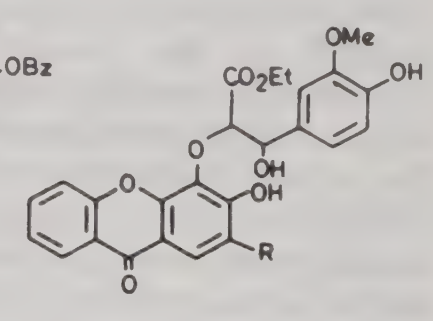

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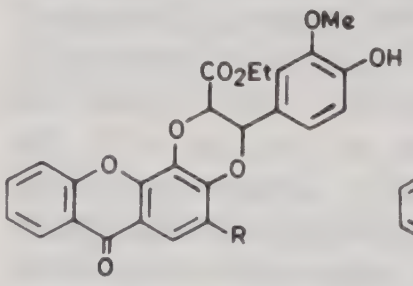

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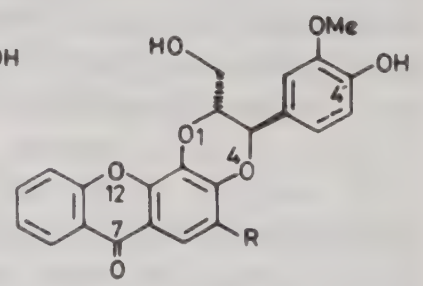

(12) R = H
(13) R = OMe

intermediates **3** and **5** were then condensed to afford ethyl 2-[9*H*(3-benzyloxy-9-oxo)xanthen-4-yl]oxy-3-oxo-3(4-benzyloxy-3-methoxyphenyl)propionate (**6**). The PMR spectrum of **6** exhibited two benzylic methylenes (δ 5.15) as a four-proton singlet, one methoxyl (δ 3.85) and a methine proton (δ 5.50) flanked by two carbonyl and one oxygen function. In the next step **6** was selectively reduced at C_3-carbonyl to afford a mixture of *erythro*- and *threo*-alcohols characterised as ethyl 2-[9*H*-(3-hydroxy-9-oxo)xanthen-4-yl]oxy-3-

†CDRI Communication No. 3854

hydroxy-3-(4-hydroxy-3-methoxyphenyl)propionate (**8**). The PMR spectrum of **8** was devoid of a methine singlet (δ 5.50) confirming the reduction of desired carbonyl function, with ester and carbonyl groups of xanthone moiety intact. The subsequent step involved in the synthesis was the intramolecular cyclisation of mixture **8** to afford the same dioxane ester (**10**); both the isomers of **8** were expected to give the same product although by different mechanisms[8]. In the final step **10** on LAH reduction afforded the desired desmethoxy-kielcorin (**12**). The PMR spectrum of **12** was similar to that of kielcorin except for the absence of methoxyl signal corresponding to C_2-OMe of xanthone moiety. The mass spectrum of **12** was characteristic of xanthonolignoid skeleton[2] and showed the molecular ion at *m/z* 406 and other peaks at *m/z* 391 (M^+-15), 374 (M^+-MeOH), 228 ($M^+-Ar-C-C-CH_2OH-$), 180 ($ArCH=CH-CH_2OH$), 137 ($ArCH_2$) and 124 (ArH).

Based on synthetic strategy employed for **12** the synthesis of kielcorin (**13**) was planned. The intermediate **5** remained the same, due to similarity of structures between **12** and **13**. The other component 3-benzyloxy-4-hydroxy-2-methoxyxanthone (**4**) was prepared by the procedure of Quiflinan and Scheinmann[9], starting from 1,2,3,4-tetramethoxy-benzene and 2-methoxybenzoyl chloride in three steps. The two halves **4** and **5** were condensed to afford **7**. The PMR spectrum of **7** displayed, in addition to usual methoxyl and aromatic protons of xanthone and vanillin part, one proton (δ 5.50) due to methine vicinal to carbonyl function. The benzylic methylenes (δ 5.00) were discernible as a four-proton singlet. Compound (**7**) was selectively reduced to afford a mixture of *erythro-* and *threo*-ethyl 2[9*H*-(3-hydroxy-2-methoxy-9-oxo)xanthen-4-yl]oxy-3-hydroxy-3(4-hydroxy-3-methoxyphenyl)propionate (**9**). The mixture of *erythro-* and *threo*-isomers was cyclised to **11**. The PMR spectrum of **11** clearly showed vicinal *trans* coupled protons of dioxane ring ($J=8.0$ Hz). Finally **11** was reduced at room temperature with LAH to afford kielcorin (**13**). The synthetic product was found indentical (m.p., m.m.p., co-TLC, IR, PMR and MS) with the natural sample.

Experimental Procedure

All melting points are uncorrected. The homogeneity of compounds was checked by TLC on silica gel G plates. The IR spectra were measured on a Perkin-Elmer 157 instrument (ν_{max} in cm^{-1}), UV spectra on Hitachi 320 instrument (λ_{max} in nm) and PMR (chemical shift in δ value) on either Varian EM 360L or Perkin-Elmer R-32 instrument using TMS as an internal standard. Mass spectra were recorded at 70 eV using Jeol JMS-D300 spectrometer. All the compounds synthesised gave satisfactory C and H analyses.

3-Benzyloxy-4-hydroxyxanthone (**3**)

To a solution of 3,4-dihydroxyxanthone (1 g) and benzyl chloride (0.46 ml) in dry acetone (150 ml) was added sodium bicarbonate (6 g) and sodium iodide (200 mg). The mixture was refluxed for 24 hr, cooled, filtered, filtrate concentrated and the residue chromatographed over silica gel. Elution of column with hexane-chloroform mixture (1:1) afforded **3**, m.p. 230° (600 mg); UV: 235, 252 and 310; IR: 3250, 1640, 1605, 1460, 1340, 1280, 1230 and 1100; PMR($CDCl_3$): 5.20 (*s*, 2H, OCH_2Ph), 6.85 (*d*, $J=9.0$ Hz, 1H, C_2-H), 7.00 (*s*, 1H, C_5-H), 7.40 (*s*, 5H, Ph), 7.90 (*d*, $J=9.0$ Hz, 1H, C_1-H), 7.65 (*m*, 2H, C_6-H, C_7-H) and 8.20 (*dd*, 1H, C_8-H); MS: *m/z* 318 (M^+).

Ethyl 2[9H-(3-benzyloxy-9-oxo)xanthen-4-yl]oxy-3-oxo-3-(4-benzyloxy-3-methoxyphenyl)propionate (**6**)

3 (577 mg) and ethyl O-benzylvanilloyl bromoacetate (**5**, 609 mg) were dissolved in dry acetone (75 ml). To this freshly fused K_2CO_3 (2.5 g) was added and the mixture refluxed for 6 hr, cooled, filtered and the filtrate concentrated to give **6** (550 mg); PMR($CDCl_3$): 1.10 (*t*, 3H, OCH_2CH_3), 3.85 (*s*, 3H, OCH_3), 4.15 (*q*, 2H, OCH_2CH_3), 5.15 (*s*, 4H, 2 $\times CH_2Ph$), 5.50 (*s*, 1H, $COCHCO_2Et$), 6.75 (*m*, 3H, $C_{2''}-H$, $C_{5''}-H$, $C_{6''}-H$), 7.20 (*s*, 10H, 2 $\times$ Ph), 6.85 (*d*, 1H, $C_{2'}-H$, $J=9.0$ Hz), 7.95 (*d*, 1H, $C_{1'}-H$, $J=9.0$ Hz), 7.60 (*m*, 3H, $C_{5'}-H$, $C_{6'}-H$, $C_{7'}-H$) and 8.15 (*dd*, 1H, $C_{8'}-H$); MS: *m/z* 644 (M^+), 418, 404, 329, 318, 241, 239, 151 and 91.

Ethyl 2[9H-(3-hydroxy-9-oxo)xanthen-4-yl]-oxy-3-hydroxy-3(4-hydroxy-3-methoxyphenyl)-propionate (**8**)

6 (200 mg) was hydrogenated over 10% Pd/C (50 mg) in absolute EtOH (20 ml) at room temperature and pressure for 48 hr. The catalyst was filtered and the filtrate concentrated to afford **8** (75 mg) as a viscous oil; PMR($CDCl_3$): 1.20 (*t*, 3H, OCH_2CH_3), 3.80 (*s*, 3H, OCH_3), 4.10 (*q*, 2H, OCH_2CH_3), 5.00 (*d*, 1H, C_2-H), 5.35 (*d*, 1H, C_3-H), 6.70 to 7.00 (*m*, 3H, $C_{2''}-H$, $C_{5''}-H$, $C_{6''}-H$), 7.20 to 7.80 (*m*, 4H, $C_{2'}-H$, $C_{5'}-H$, $C_{6'}-H$, $C_{7'}-H$), 7.88 (*d*, 1H, $C_{1'}-H$) and 8.15 (*dd*, 1H, $C_{8'}-H$); MS: *m/z* 466 (M^+), 451, 447, 401, 375, 330, 313, 240 and 228.

2,3-Dihydro-2-ethoxycarbonyl-3-(4-hydroxy-3-methoxyphenyl)-7H-1,4-dioxino-[2,3-c]xanthen-7-one (**10**)

A mixture of **8** (50 mg) and distilled $POCl_3$ (3 ml) was heated at 40° for 30 min, cooled, poured onto ice and extracted with ethyl acetate (3 $\times$ 50 ml). The organic layer was washed with 10% aq $NaHCO_3$, water and the

solvent removed to furnish pure **10** (40 mg); PMR($CDCl_3$): 1.10 (*t*, 3H, OCH_2CH_3), 3.80 (*s*, 3H, OCH_3), 4.10 (*q*, 2H, OCH_2CH_3), 4.85 (*d*, 1H, C_2-H, $J=9.0$ Hz), 5.20 (*d*, 1H, C_3-H, $J=9.0$ Hz), 6.95 (*d*, 1H, C_5-H), 6.85 (*m*, 3H, $C_{2'}-H$, $C_{5'}-H$, $C_{6'}-H$), 7.30 to 7.70 (*m*, 3H, C_5-H, $C_{10}-H$, $C_{11}-H$), 7.80 (*d*, 1H, C_6-H) and 8.25 (*dd*, 1H, C_8-H); MS: *m/z* 448 (M^+), 403, 375, 279, 228, 147 and 91.

2,3-*Dihydro*-3-(4-*hydroxy*-3-*methoxyphenyl*)-2-*hydroxymethyl*-7*H*-1,4-*dioxino*-[2,3-*c*]*xanthen*-7-*one* (*desmethoxy*-*kielcorin*, **12**)

A suspension of **10** (10 mg) and LAH (50 mg) in dry THF (25 ml) was stirred for 2 hr. Excess of LAH was decomposed with ethyl acetate, the organic layer washed with water, dried (Na_2SO_4) and concentrated to afford **12** as a viscous product (6 mg); PMR($CDCl_3$): 3.60 (*m*, 2H, CH_2OH), 3.85 (*s*, 3H, OCH_3), 4.95 (*d*, 1H, C_2-H, $J=9.0$ Hz), 5.10 (*d*, 1H, C_3-H, $J=9.0$ Hz), 6.70 to 7.00 (*m*, 3H, $C_{2'}-H$, $C_{5'}-H$, $C_{6'}-H$), 7.30 to 7.70 (*m*, 3H, C_9-H, $C_{10}-H$, $C_{11}-H$) and 8.25 (*dd*, 1H, C_8-H); MS: *m/z* 406 (M^+), 351, 374, 228, 180 and 149.

3-*Benzyloxy*-4-*hydroxy*-2-*methoxyxanthone* (**4**)

A mixture containing 3,4-dihydroxy-2-methoxyxanthone (**2**, 500 mg) in dry acetone (100 ml), benzyl chloride (0.2 ml), sodium iodide (100 mg) and sodium bicarbonate (2.5 g) was refluxed for 8 hr, cooled and filtered. The residue obtained after removal of solvent from the filtrate, was chromatographed over silica gel. elution with $CHCl_3$-hexane (1:3) gave 3,4-dibenzyloxy-2-methoxyxanthone, m.p. 210°. Further elution of column with $CHCl_3$-hexane (1:1) afforded **4** (300 mg), m.p. 230°; PMR($CDCl_3$): 3.85 (*s*, 3H, OCH_3), 5.10 (*s*, 2H, OCH_2Ph), 8.15 (*dd*, 1H, C_8-H) and 7.15 to 7.50 (*m*, 9H, Ar-protons); MS: *m/z* 362 (M^+), 257 and 91.

Ethyl 2[9*H*-(3-*benzyloxy*-2-*methoxy*-9-*oxo*)-*xanthen*-4-*yl*]*oxy*-3-*oxo*-3(4-*benzyloxy*-3-*methoxyphenyl*)*propionate* (**7**)

A mixture containing **4** (300 mg), **5** (400 mg), dry acetone (75 ml) and freshly fused K_2CO_3 (2.5 g) was refluxed for 12 hr. After usual work-up **7** (500 mg) was obtained as an oily residue: PMR($CDCl_3$): 1.10 (*t*, 3H, OCH_2CH_3), 3.85 (*s*, 6H, $2\times OCH_3$), 4.20 (*q*, 2H, OCH_2CH_3), 5.00 (*s*, 4H, $2\times OCH_2Ph$), 5.50 (*s*, 1H, C_2-H), 6.70 to 7.00 (*m*, 3H, $C_{2''}-H$, $C_{5''}-H$, $C_{6''}-H$), 7.30 (*s*, 10H, $2\times OCH_2Ph$), 7.30 to 7.70 (*m*, 4H, $C_{1'}-H$, $C_{5'}-H$, $C_{6'}-H$, C_7-H) and 8.25 (*dd*, 1H, C_8-H); MS: *m/z* 674 (M^+), 656, 608, 502, 470, 434, 384, 338, 328, 241 and 91.

Ethyl 2-[9*H*-(3-*hydroxy*-2-*methoxy*-9-*oxo*)-*xanthen*-4-*yl*]*oxy*-3-*hydroxy*-3-(4-*hydroxy*-3-*methoxyphenyl*)*propionate* (**9**)

A solution of **7** (250 mg) in absolute EtOH (20 ml) containing 10% Pd/C (50 mg) was hydrogenated at room temperature for 48 hr. The catalyst was filtered and the filtrate on concentration provided **9** (100 mg) as an oily mass; PMR($CDCl_3$): 1.20 (*m*, 3H, OCH_2CH_3), 3.85 (*s*, 6H, $2\times OCH_3$), 4.20 (*m*, 2H, OCH_2CH_3), 4.80 (*d*, 1H, C_2-H), 5.45 (*d*, 1H, C_3-H), 6.80 (*m*, 3H, $C_{2''}-H$, $C_{5''}-H$, $C_{6''}-H$), 7.50 (*m*, 4H, $C_{1'}-H$, $C_{5'}-H$, $C_{6'}-H$, C_7-H) and 8.20 (*dd*, 1H, C_8-H); MS: *m/z* 496 (M^+), 472, 454, 430, 405, 257, 241, 177 and 151.

2,3-*Dihydro*-2-*ethoxycarbonyl*-3-(4-*hydroxy*-3-*methoxyphenyl*)-5-*methoxy*-7*H*-1,4-*dioxino*-[2,3-*c*]*xanthen*-7-*one* (**11**)

A mixture of **9** (50 mg) and $POCl_3$ (5 ml) was heated at 40° for 30 min, cooled, poured onto ice and extracted with ethyl acetate (3×25 ml). The organic layer was washed with aq $NaHCO_3$, dried (Na_2SO_4) and evaporated to afford **11** (30 mg); PMR($CDCl_3$): 1.30 (*m*, 3H, OCH_2CH_3), 3.90 (*s*, 6H, $2\times OCH_3$), 4.20 (*m*, 2H, OCH_2CH_3), 6.90 (*m*, 3H, $C_{2'}-H$, $C_{5'}-H$, $C_{6'}-H$), 7.50 (*m*, 4H, C_6-H, $C_{10}-H$, $C_{11}-H$) and 8.20 (*dd*, 1H, C_8-H); MS: *m/z* 478 (M^+), 456, 455, 369, 257, 177 and 151.

2,3-*Dihydro*-3-(4-*hydroxy*-3-*methoxyphenyl*)-2-*hydroxymethyl*-5-*methoxy*-7*H*-1,4-*dioxino*-[2,3-*c*]*xanthen*-7-*one* (*kielcorin*, **13**)

A solution of **11** (30 mg) in dry THF (30 ml) was stirred with LAH (100 mg) for 2 hr to furnish **13**, m.p. 254° (15 mg); PMR($CDCl_3$): 3.60 (*m*, 2H, CH_2OH), 3.85 (*s*, 3H, OCH_3), 3.90 (*s*, 3H, OCH_3), 4.20 (*m*, 1H, C_2-H, $J=9.0$ Hz), 5.10 (*d*, 1H, C_3-H, $J=9.0$ Hz), 6.80 to 7.00 (*m*, 3H, $C_{2'}-H$, $C_{5'}-H$, $C_{6'}-H$), 7.20 to 7.60 (*m*, 3H, C_9-H, $C_{10}-H$, $C_{11}-H$), 7.22 (*s*, 1H, C_6-H) and 8.25 (*dd*, 1H, C_8-H); MS: *m/z* 436 (M^+), 418, 299, 272, 257, 243, 180 and 137.

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Reaction of Anthrone with Propargyl Bromide: A Novel Synthesis of 2-Methylanthra[9,1-*bc*]pyran

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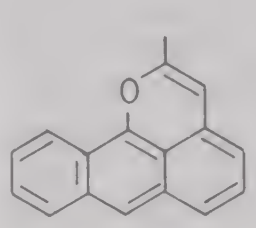
Reaction of anthrone with propargyl bromide in alcoholic potassium hydroxide affords 2-methylanthra[9,1-*bc*]pyran (V) and 10-propargylanthrone (VI) in good yields.

Four different groups[1-4] have studied the base-catalysed alkylation of anthrone (I) with alkyl halides. In brief the results were the formation of preponderent C-alkylated products followed by O-alkylation of the resulting C-alkylated anthrone (see Scheme 1).

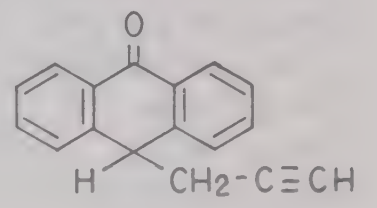
We became interested in studying the molecular transformation of anthracene 9-propynyl ether and to synthesise this compound we treated I with propargyl bromide in alcoholic potassium hydroxide for 4 hr under nitrogen. Two products, viz. V (m.p. 210°; yield 35%) and VI (m.p. 130°; yield 37%) separated by chromatography over silica gel, were obtained. The IR spectrum of V in KBr did not exhibit any peak assignable to $\nu C=O$, present in the starting I. Its 60 MHz PMR spectrum in DMSO-d_6 displayed a three-proton singlet at δ 3.2 and a nine-proton multiplet in the aromatic region δ 7.35-8.35, and no signal due to acetylenic protons.

The structure of V was further corroborated by its mass spectrum (Scheme 2). Similar processes have been postulated[5] for the fragmentation of 2-methylbenzofuran.

The IR spectrum of the product (VI) in KBr exhibited $\nu C=O \sim 1670$ cm^{-1}. Its 90 MHz PMR spectrum in $CDCl_3$ displayed a one-proton triplet at δ 1.90-1.95 assignable to acetylenic proton, a two-proton multiplet at 2.80-2.90 due to CH_2 protons, a one-proton triplet at 4.40-4.55 due to benzylic proton



V



VI

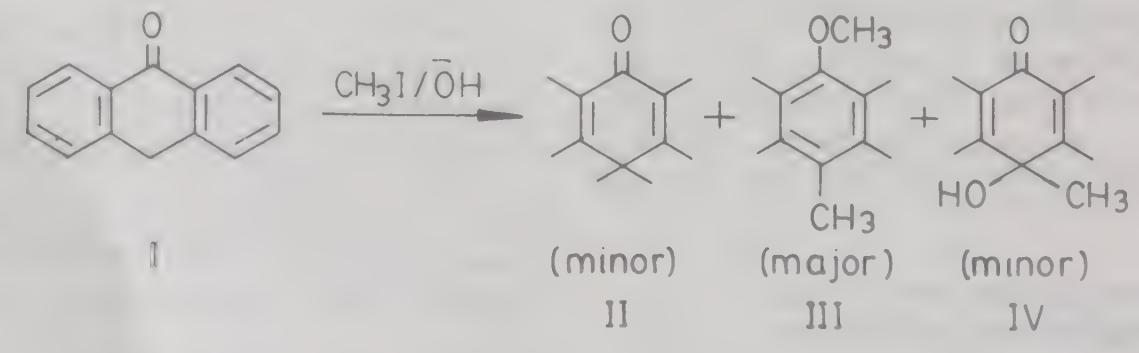
and two multiplets for aromatic protons at 7.32-7.85 (6H) and 8.35-8.50 (2H). The structure (VI) was further corroborated by its mass spectral data.

The formation of V can be explained through the Claisen rearrangement of the intermediate anthracene 9-propargyl ether (VII, not isolated) followed by a [1,2] shift of the allenyl group, cyclization and isomerization (Scheme 3).

Literature[6] support is available for steps (1) and (2) in the conversion of mesityl propynyl ether to 2,4,6 trimethyl-3-allenylphenol. It is striking that V is formed in the alkylation reaction under such a mild condition.

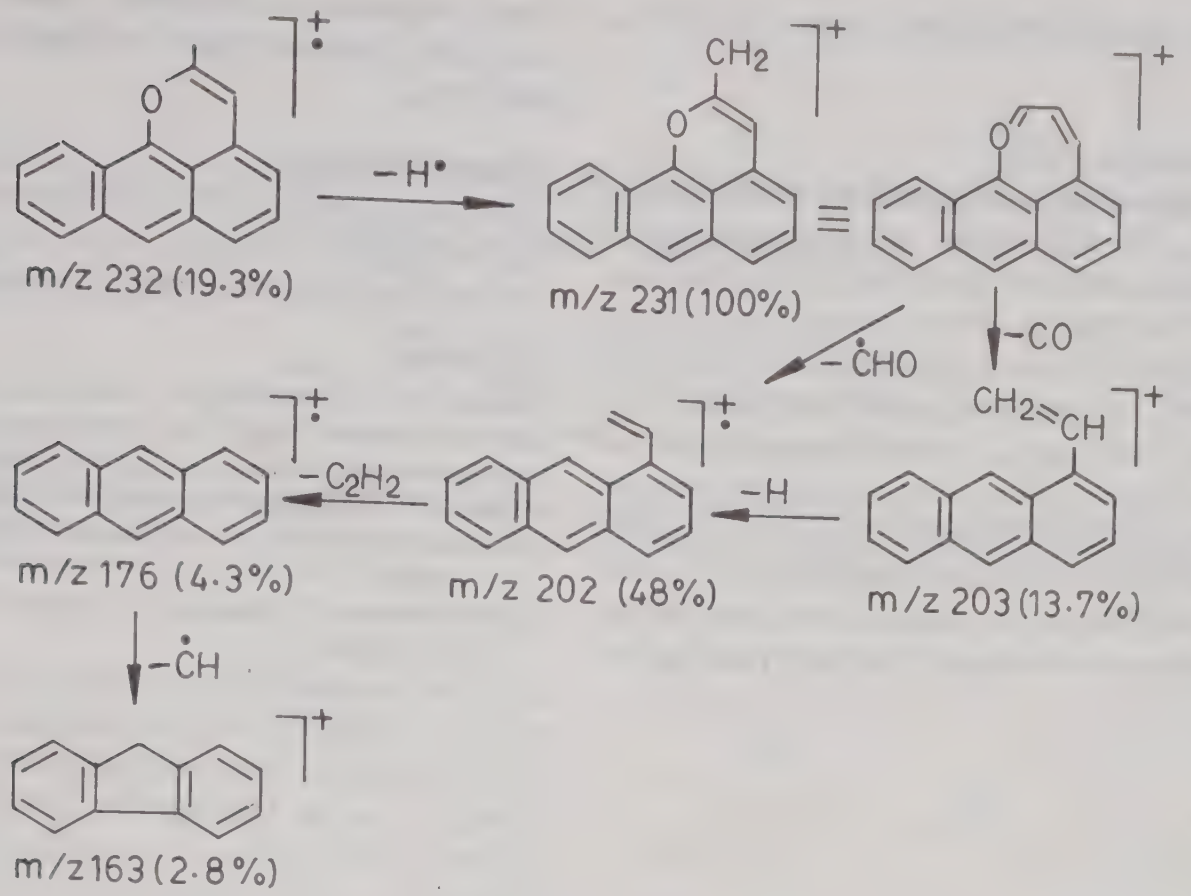
Experimental Procedure

The melting points are uncorrected. PMR spectra were recorded on a Varian instrument using $CDCl_3$ or DMSO-d_6 as solvent and TMS as an internal standard. Infrared spectra (IR) were recorded in KBr pellets.

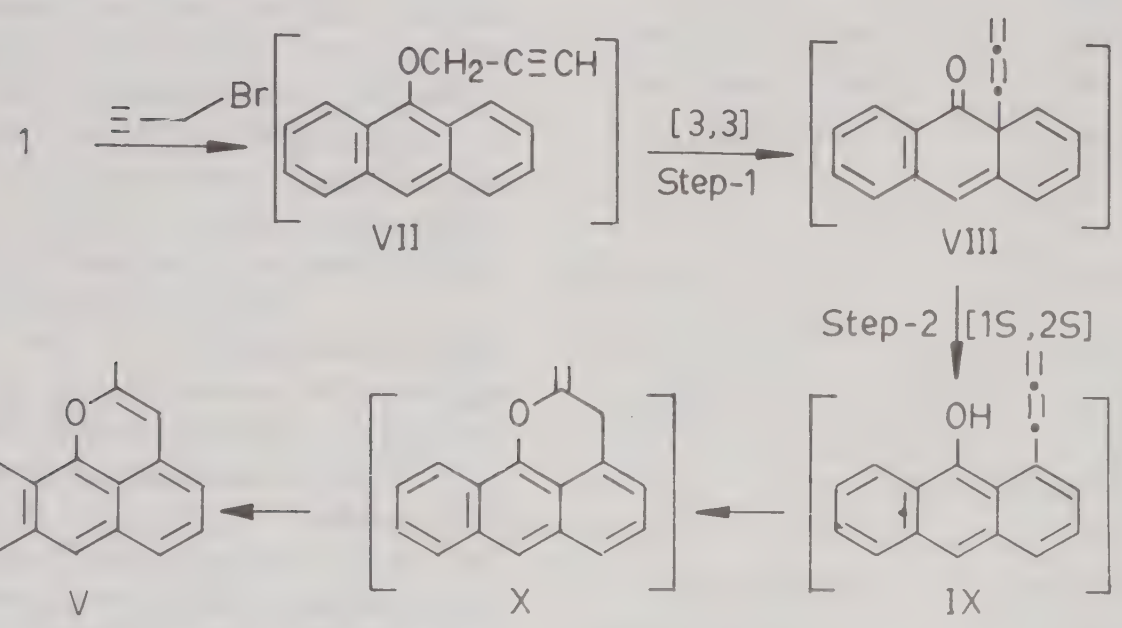


I (minor) II (major) III (minor) IV

Scheme 1



Scheme 2



Scheme 3

2-*Methylanthra*[9,1-*bc*]*pyran* (*V*)

To a stirred solution of anthrone (I, 0.01 mol) in ethanol (90%, 60 ml) was added potassium hydroxide (0.01 mol) and the mixture was refluxed for 30 min under nitrogen. Propargyl bromide (0.01 mol) in ethanol (90%, 10 ml) was added dropwise to the above reaction mixture and refluxing under nitrogen was continued for 4 hr more. Ethanol was removed and the residue extracted with chloroform. The chloroform extract was washed with saturated brine, water and dried (Na_2SO_4). Removal of solvent gave a mixture of two products, which were separated by chromatography over silica gel. Elution of the column with pet. ether (60-80°)–benzene (4:1) (10 × 20 ml portions) afforded VI as a white solid, m.p. 130°, yield 37%; IR (KBr): 3250 (−C≡C−H), 1670 (>C=O) and 2030 cm^{-1} (−C≡C); PMR ($CDCl_3$, 90 MHz): δ 1.90-1.95 (*t*, 1H), 2.80-2.90 (*m*, 2H), 4.40-4.55 (*t*, 1H), 7.32-7.85 (*m*, 6H), 8.35-8.50 (*m*, 2H); MS: *m/z* 232 (M^+), 231, 194, 193 (100%), 165, 152 etc. (Found: C, 87.6; H, 5.1. $C_{17}H_{12}O$ requires C, 87.9; H, 5.2%).

Compound V was obtained by eluting the column with pet. ether (60-80°)-benzene (1:1) (6 × 20 ml portions) as a white solid, yield 35%, m.p. 210° (Found: C, 87.4; H, 5.1. $C_{17}H_{12}O$ requires C, 87.9; H, 5.2%); IR (KBr): 1320 (ether) and 3100 cm^{-1} (aromatic C−H);

PMR (DMSO-d_6; 60 MHz): 3.20 (*s*, 3H), 7.35-8.35 (*m*, 9H).

10-*Propargylanthrone* (*VI*)

To a stirring solution of anthrone (0.01 mol) in ethanol (90%, 90 ml) under nitrogen was added potassium hydroxide (0.01 mol) and the mixture was heated to 70° for 30 min. The mixture was cooled to room temperature and propargyl bromide (0.01 mol) in ethanol (90%, 10 ml) was added dropwise to it. Stirring under nitrogen at room temperature was continued for further 14 hr. After removal of ethanol, the residue was extracted with chloroform, washed with saturated brine, water and dried (Na_2SO_4). After removal of chloroform, the product was purified by chromatography over silica gel. Careful crystallisation from chloroform furnished 10-propargylanthrone, m.p. 130°, yield 60% and anthraquinone, m.p. 280°, yield 10%.

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Synthesis of (±)-Isoboldine & (±)-2′-Amino & Nitro Derivatives of Reticuline & Laudanidine†

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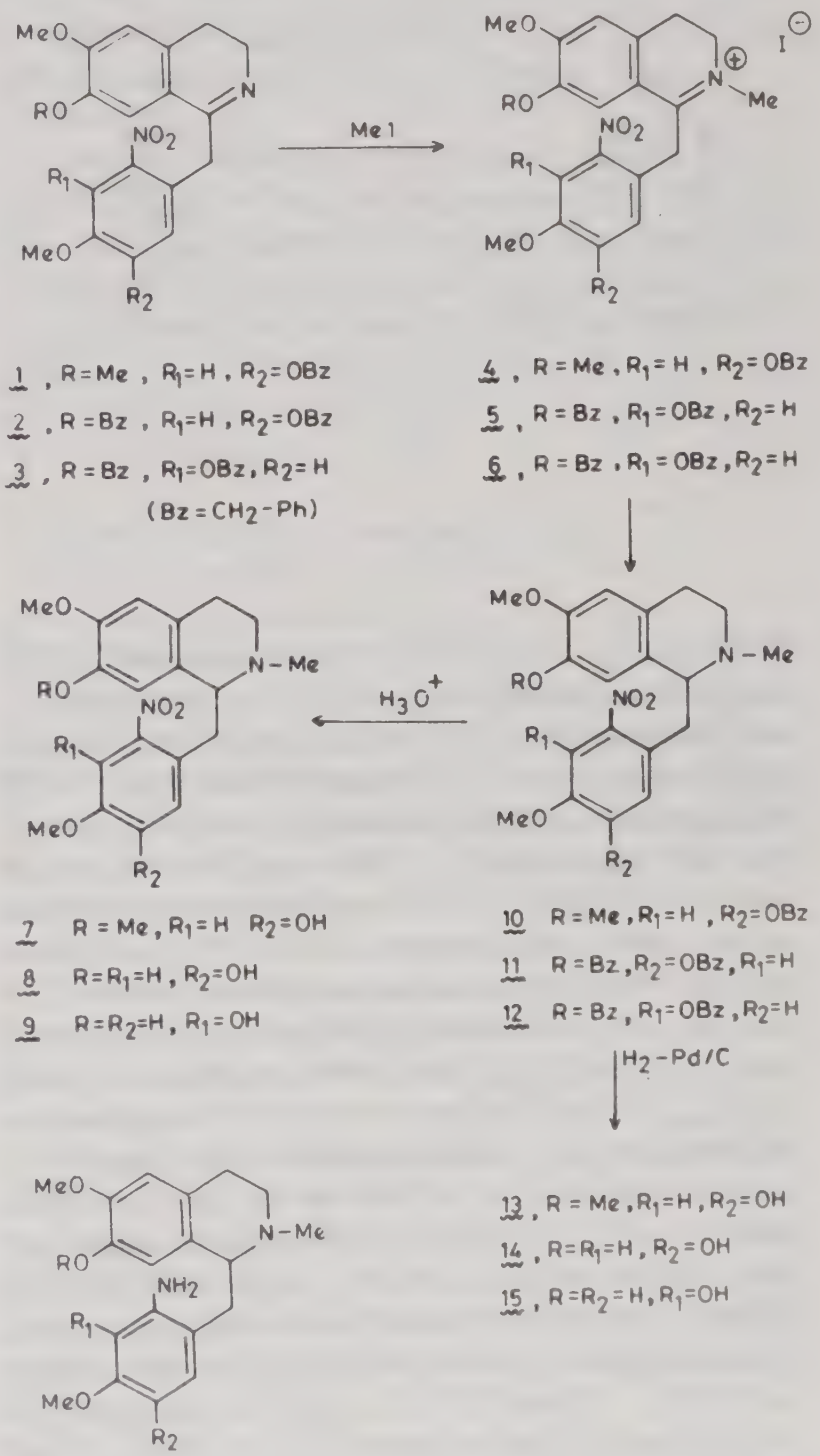
(±)-2′-Nitro and amino derivatives of reticuline and laudanidine and aporphine alkaloid, isoboldine have been synthesized. Pschorr cyclisation of (±)-2′-amino-O,O′-dibenzylreticuline yields (±)-O,O′-dibenzylisoboldine, O,O′-dibenzylreticuline and O-benzylisosalutaridine.

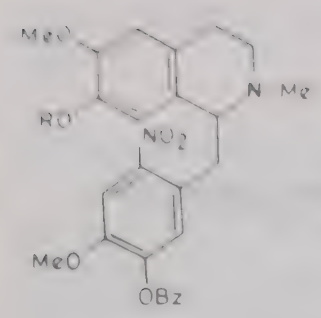
Substituted 1-benzyltetrahydroisoquinolines are important intermediates in the 'aberrant biosynthesis'[1] of 1-benzyltetrahydroisoquinoline derived alkaloids. Suitably substituted amino 1-benzyltetrahydroisoquinolines are employed for the synthesis of aporphine alkaloids[2,3]. The syntheses of (±)-2′-nitroreticulines (**8**) and (**9**). (±)-2′-nitrolaudanidine (**7**), (±)-2′-aminoreticulines (**14**) and (**15**) and (±)-2′-aminolaudanidine (**13**) and the aporphine alkaloid (±)-isoboldine (**22**) are reported in the present paper. The antifungal and antibacterial activities of the compounds synthesized and the characterization of the compounds formed during Pschorr cyclisation of (±)-2′-amino-O,O′-dibenzylreticuline (**17**) and (±)-2′-amino-O-benzyllaudanidine (**16**) also form the subject of this paper.

The methiodides (**4-6**) of 3,4-dihydroisoquinolines (**1-3**)[4-7] respectively on reduction with sodium borohydride afforded the corresponding tetrahydroisoquinolines (**10-12**). Hydrogenolysis of **10-12** led to (±)-2′-nitrolaudanidine (**7**) and (±)-2′-nitroreticulines (**8**) and (**9**) respectively. The lone proton *ortho* to NO_2 group in **7**, **8**, **10** and **11** was highly deshielded and appeared at δ 7.4 in their PMR spectra. The two *ortho*-coupled protons in **9** and **12** resonated as two doublets (J=9.5 Hz). Catalytic (10% Pd/C) hydrogenation of **10-12** resulted in (±)-2′-aminolaudanidine (**13**), and (±)-2′-aminoreticulines (**14**) and (**15**) respectively. The C_3–H in **13** and **14** resonated upfield and appeared at δ 6.1. The corresponding proton in the nitro compounds (**7**, **8**, **10**, **11**) appeared at δ 7.4. Reduction of **10** and **11** separately with Zn and AcOH afforded the nitro-reduced products (±)-2′-amino-O-benzyllaudanidine[5] (**16**) and (±)-2′-amino-O,O′-dibenzylreticuline (**17**) respectively, the protecting benzyloxy groups remaining unaffected.



Pschorr cyclisation of **17** in the presence of Cu gave a mixture of compounds. Resolution of the mixture on silica gel preparative TLC plates furnished (±)-1,9-

†CDRI communication No. 3852



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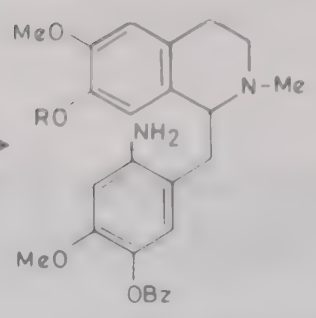
11 , R = Bz



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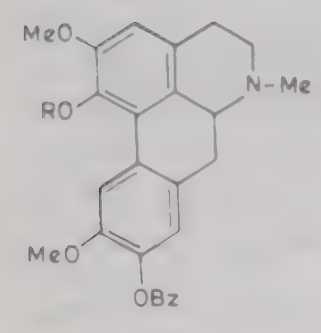

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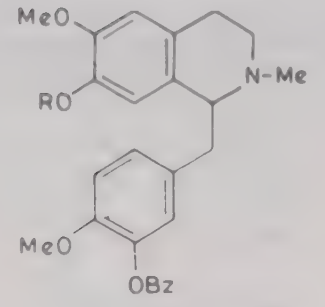

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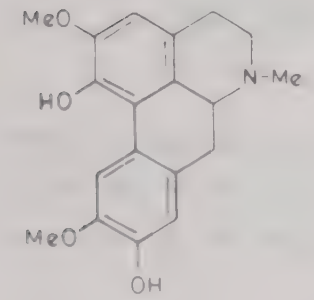
21 , R = Me



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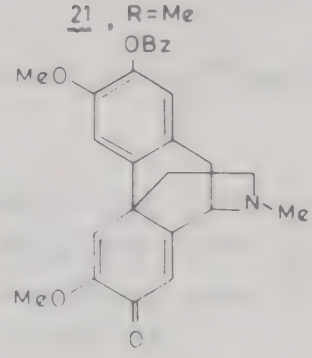

23

dibenzyloxy-2,10-dimethoxy-6-methylaporphine (**18**) (O,O-dibenzylisoboldine) (8.2%), 1-(3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-benzyloxy-2-methylisoquinoline (O,O-dibenzylreticuline)[6,8] (**20**) (20.6%) and (±)-O-benzylisosalutaridine[9] (**23**) (12.6%). The UV spectrum (λ_{max} 280 and 303 nm) of **18** indicated a typical 1,2,9,10-tetraoxygenated aporphine pattern which was supported by its PMR and mass spectra. The C-11 proton resonated downfield at δ 7.9 and the other aromatic protons were in the normal position. The IR (ν_{max} 1665, 1644 and 1623 cm^{-1}) and UV (λ_{max} 236 and 281 nm) spectra of **23** suggested the presence of a cross-conjugated α-methoxy-cyclohexadienone system in the molecule. The PMR spectrum of **23** in $CDCl_3$ exhibited three singlets of three protons each at δ 2.38 (N – Me), 3.73 (OMe), 3.82 (OMe), a two-proton singlet due to methylene protons of the benzyloxy function and two one-proton singlets at 6.81 ($C_5 - H$) and 6.27 ($C_8 - H$). The seven protons in the aromatic region appeared at 6.33 (1H, *s*), 6.65 (1H, *s*), and 7.34 (5H, *bs*, $O - CH_2 - C_6H_5$). The mass fragmentation of **23** had molecular ion peak at *m/z* 417, the other prominent peaks appearing at *m/z* 402, 360, 326, 298, 283, 269 and 91. The compound (**18**) was found identical with (±)-O,O′-dibenzylreticuline[6] by comparison of PMR and mass spectral data, co-TLC and mixed m.p. with an authentic sample.

Pschorr cyclisation of (±)-2′-amino-O-benzyllaudanidine (**16**) under the conditions as above gave (±)-O-benzyllaudanidine[9] (**21**) (±)-O-benzyl-N-methyllaurotetanine[9] (**19**) and the compound (**23**). It is interesting to note that in the formation of **23** from **16** the methoxy group at position-7 in **16** got demethylated.

(±)-Isoboldine[10] (**22**) was finally prepared in 66% yield by hydrogenolysis of **18** with hydrochloric acid. The IR, UV, PMR and mass spectra and elemental analyses of the compound prepared, were in complete agreement with the assigned structure.

(±)-2′-Nitrolaudanidine (**7**)-2′-nitroreticulines (**8**) and (**9**)-2′-aminolaudanidine (**13**) and 2′-amino-reticulines (**14**) and (**15**) when tested *in vitro* against the bacteria *Streptococcus faecalis*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* and against the fungi *Candida albicans*, *Cryptococcus neoformans*, *Chlorotrichum schenckii*, *Trichophyton mentagrophytes* and *Aspergillus fumigatus* did not show any significant activity.

Experimental Procedure

Melting points were taken in a H_2SO_4 bath and are uncorrected. The compounds were routinely checked by TLC, IR(KBr), UV(MeOH), PMR and MS for purity and confirmation of the assigned structures. All the new compounds gave satisfactory C, H and N analyses (± 0.4% for C; ± 0.5% for H; and 0.5% for N).

1-(5-*Benzyloxy*-4-*methoxy*-2-*nitrobenzyl*)-6,7-*dimethoxy*-3,4-*dihydroisoquinoline methiodide* (**4**)

The free base (**1**) from 3,4-dihydroisoquinoline[5] (**1**). HCl was prepared as usual. A mixture of **1** (3.6 g), dry $CHCl_3$ (5 ml), dry C_6H_6 (1 ml) and MeI (30 ml) was kept at room temperature for 2 days. The excess of solvent and the reagent were removed *in vacuo* to give a residue, which was triturated with $CHCl_3 - Et_2O$ to afford **4**, yield 3.3 g (70%), m.p. 187-88° (d) ($CHCl_3 - Et_2O$) [lit.[5] m.p. 190° (d)]. Similarly were prepared the methiodides, 1-(5-benzyloxy-4-methoxy-2-nitrobenzyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline methiodide (**6**) from **3** [m.p. 170-71° ($CHCl_3 - Et_2O$); lit.[7] m.p. 172°].

1-(5-*Benzyloxy*-4-*methoxy*-2-*nitrobenzyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (**10**)

To an ice-cooled stirred solution of **4** (4 g) in MeOH (300 ml), $NaBH_4$ (2 g) was added portionwise and the stirring continued for 2 hr at room temperature. The

solvent was removed *in vacuo*, the residue extracted with $CHCl_3$, the organic extract washed with water, dried (Na_2SO_4) and the solvent evaporated to give **10**, yield, 2.7 g (85%), m.p. 108-10° (Et_2O-hexane); IR(KBr): 1508, 1325 (NO_2) cm^{-1}; PMR($CDCl_3$): δ 2.24 (*s*, 3H, N$-CH_3$), 3.61, 3.70, 3.79 (*s*, 3H each, 3×O$-CH_3$), 4.90 (*s*, 2H, O$-CH_2-C_6H_5$), 6.30 (*s*, 1H, Ar$-H$), 6.40 (*s*, 2H, Ar−H), 7.23 (*bs*, 5H, O$-CH_2C_6H_5$), 7.42 (*s*, 1H, Ar$-H$, *ortho* to NO_2 group).

1-(5-*Benzyloxy*-4-*methoxy*-2-*nitrobenzyl*)-7-*benzyloxy*-6-*methoxy*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (**11**)

It was prepared from **5** by the procedure described above, yield 80%, m.p. 114-15° (Et_2O-hexane); IR(KBr): 1500 and 1315 (NO_2) cm^{-1}; PMR($CDCl_3$): δ 2.23 (*s*, 3H, N$-CH_3$), 3.71, 3.79 (*s*, 3H each, 2×O$-CH_3$), 4.83, 4.488 (*s*, 2H each, 2×O$-CH_2-C_6H_5$), 6.30, 6.37, 6.43 (each *s*, 1H each, 3H, Ar$-H$), 7.27 (*bs*, 10H, 2×O$-CH_2-C_6H_5$), 7.42 (*s*, 1H, Ar−H, *ortho* to NO_2 group).

1-(3-*Benzyloxy*-4-*methoxy*-2-*nitrobenzyl*)-7-*benzyloxy*-6-*methoxy*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (**12**)

It was prepared from **6** by the procedure as described above, yield 78%; IR(neat): 1520 and 1360 (NO_2) cm^{-1}; PMR($CDCl_3$): δ 2.23 (*s*, 3H, N$-CH_3$), 3.69 (*s*, 6H, 2×O$-CH_3$), 4.84, 4.99 (*s*, 2H each, 2×O$-CH_2-$Ph), 6.25, 6.42 (*s*, 1H each, 2H, Ar−H), 6.56 (*d*, J=9 Hz, 1H, Ar$-H$), 6.72 (*d*, J=9 Hz, 1H, Ar$-H$), 7.24 (*bs*, 10H, 2×O$-CH_2-C_6H_5$).

1-(5-*Hydroxy*-4-*methoxy*-2-*nitrobenzyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (**7**) [(±)-2′-*nitrolaudanidine*]

A mixture containing **10** (2 g), EtOH (60 ml) and 12 *N* HCl (60 ml) was heated under reflux for 4 hr. The excess of solvent and the reagent were removed *in vacuo* to furnish **7**.HCl, yield 1.5 g (85%), m.p. 165-66° (MeOH-ether); IR(KBr): 3400 (OH), 1515 and 1315 (NO_2) cm^{-1}; PMR($CDCl_3$ + DMSO-d_6): δ 2.24 (*s*, 3H, N$-CH_3$), 3.58, 3.68, 3.71 (*s*, 1H each, Ar$-H$), 7.40 (*s*, 1H, Ar$-H$, *ortho* to NO_2 group).

1-(5-*Hydroxy*-4-*methoxy*-2-*nitrobenzyl*)-7-*hydroxy*-6-*methoxy*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (**8**) [(±)-2′-*nitroreticuline*]

8 was prepared from **11** as **8**.HCl by the procedure described above, yield 73%, m.p. 185-86° (MeOH-ether); IR(KBr): 3400 (OH), 1520 and 1335 (NO_2) cm^{-1}; PMR($CDCl_3$ + DMSO-d_6): δ 2.24 (*s*, 3H, N$-CH_3$), 3.67, 3.70 (*s*, 3H each, 2×O$-CH_3$), 6.30, 6.47, 6.49 (*s*, 1H each, Ar$-H$), 7.45 (*s*, 1H, Ar$-H$, *ortho* to NO_2 group).

1-(3-*Hydroxy*-4-*methoxy*-2-*nitrobenzyl*)-7-*hydroxy*-6-*methoxy*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (**9**) [(±)-2′-*nitroreticuline*]

9 was prepared from **12** as **9**.HCl by the method described above, yield 76%, m.p. 159-60° (MeOH-ether); IR(KBr): 3400 (OH), 1525 and 1360 (NO_2) cm^{-1}; PMR($CDCl_3$ + DMSO-d_6): δ 2.21 (*s*, 3H, N$-CH_3$), 3.67, 3.69 (*s*, 3H each, 2×O$-CH_3$), 6.20, 6.32 (*s*, 1H each, Ar$-H$), 6.51 (*d*, J=9.5 Hz, 1H, Ar$-H$), 6.65 (*d*, J=9.5 Hz, 1H, Ar$-H$).

1-(2-*Amino*-5-*hydroxy*-4-*methoxybenzyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (**13**) [(±)-2′-*aminolaudanidine*]

A mixture containing **10** (500 mg), MeOH (50 ml) and 10% Pd/C (150 mg) was kept under H_2 at 50 psi for 3 hr. The catalyst was filtered off and the filtrate concentrated *in vacuo* to afford **13**, yield 250 mg (67%), m.p. 145-46° (ether-hexane); IR(KBr): 3400 (OH and NH_2) cm^{-1}; PMR($CDCl_3$): δ 2.40 (*s*, 3H, N$-CH_3$), 3.56, 3.70, 3.73 (*s*, 3H each, 3×O$-CH_3$), 6.13 (*s*, 2H, Ar$-H$), 6.46 (*s*, 2H, Ar$-H$).

1-(2-*Amino*-5-*hydroxy*-4-*methoxybenzyl*)-7-*hydroxy*-6-*methoxy*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (**14**) [(±)-2′-*aminoreticuline*]

14 was prepared from **11** by the procedure described above, yield 65%, m.p. 125° (d) (ether-hexane); IR(KBr): 3400 (OH and NH_2) cm^{-1}; PMR($CDCl_3$ + DMSO-d_6): δ 2.31 (*s*, 3H, N$-CH_3$), 3.64, 3.68 (*s*, 3H each, 2×O$-CH_3$), 6.18, 6.30 (*s*, 1H each, Ar−H), 6.40 (*s*, 2H, Ar−H).

1-(2-*Amino*-3-*hydroxy*-4-*methoxybenzyl*)-7-*hydroxy*-6-*methoxy*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (**15**) [(±)-2′-*aminoreticuline*]

15 was prepared from **12** by the procedure as described for **13**, yield 71%, m.p. 147-48° (ether-hexane); IR(KBr): 3350 (OH and NH_2) cm^{-1}; PMR ($CDCl_3$ + DMSO-d_6): δ 2.31 (*s*, 3H, N$-CH_3$), 3.61, 3.66 (each *s*, 3H each, 2×O$-CH_3$), 6.17 (*d*, J=9 Hz, 1H, Ar$-H$), 6.21 (*d*, J=9 Hz, 1H, Ar$-H$), 6.38 (*s*, 2H, Ar$-H$).

1-(2-*Amino*-5-*benzyloxy*-4-*methoxybenzyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (**16**) [(±)-*O*-*benzyl*-6′-*aminolaudanidine*]

16 was prepared from **10** by reduction with Zn/AcOH, yield 230 mg (84%), m.p. 74-75° (ether-hexane) (lit.[5] m.p. 75-77°); PMR($CDCl_3$): δ 2.40 (*s*, 3H, $N-CH_3$), 3.52, 3.69, 3.72 (*s*, 3H each, $3\times O-CH_3$), 4.82 (*s*, 2H, $O-CH_2-C_6H_5$), 6.05, 6.12, 6.33, 6.41 (*s*, 1H each, Ar–*H*), 7.23 (*bs*, 5H, $O-CH_2-C_6-H_5$).

1-(2′-Amino-5-benzyloxy-4-methoxybenzyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydro-2-methylisoquinoline (**17**)
[(±)-*O,O′-Dibenzyl-2′-aminoreticuline*]

To a stirred solution of **11** (500 mg) in AcOH (20 ml), Zn dust (4.5 g) was added in portions at 5° and the stirring continued for 10 min at 10-15°. The unreacted Zn was filtered off and the filtrate basified with 10% NH_3 solution, extracted with $CHCl_3$, washed with water, dried (Na_2SO_4) and the solvent removed *in vacuo* to give **17**, which was used in the next step as such.

Pschorr cyclisation of **17**

Compound (**17**, 300 mg) in MeOH (2.5 ml) (cooled to 0°) was treated with a mixture of conc. H_2SO_4 (0.5 ml) and MeOH (2.5 ml) at 0°. To this, a solution of $NaNO_2$ (100 mg) in water (6 ml) was slowly added at 0° and left overnight at 3-5°; freshly prepared catalytic copper (200 mg) was added and when a vigorous evolution of N_2 took place. After stirring for 1 hr at room temperature, the suspension was boiled for 30 min. The cooled reaction mixture was treated with water (15-20 ml) and extracted with ether (4 × 25 ml). The aqueous layer was basified with 10% NH_3 solution, extracted with ether, washed with water, dried (Na_2SO_4) and evaporated to afford a mixture of compounds which were purified on silica gel preparative plates using 4% MeOH–$CHCl_3$ solvent system to give **18**, **20**, **23**.

(±)-*O,O′-Dibenzylisoboldine* (**18**) yield 24 mg (8.2%); PMR($CDCl_3$): δ 2.41 (*s*, 3H, $N-CH_3$), 3.70, 3.77 (*s*, 3H each, $2\times O-CH_3$), 4.88, 5.08 (*s*, 2H each, $2\times O-CH_2-C_6H_5$), 6.50, 6.70 (*s*, 1H, Ar–*H*), 7.15-7.50 (*m*, 10H, $2\times O-CH_2-C_6H_5$), 7.90 (*s*, 1H, Ar–*H*, $C_{11}-H$); MS: *m/z* 507 (M^+), 506 (M^+-1), 416 (M^+-91), 492 (M^+-15), 476 (M^+-31), 373, 325, 282, 267, 227, 191, 91.

(±)-*O,O′-Dibenzylreticuline* (**20**): yield 60 mg (20.6%), m.p. 90-91° (ether-hexane) (lit.[6] m.p. 89°; an oil[8]); IR(KBr): 1623 cm^{-1}; UV(MeOH): 236 and 281 nm; PMR($CDCl_3$): δ 2.38 (*s*, 3H, $N-CH_3$), 3.73, 3.82 (*s*, 3H each, $2\times O-CH_3$), 5.06 (*s*, 2H, $O-CH_2-C_6H_5$), 6.27 (*s*, 1H, C_8-H), 6.33 (*s*, 1H, Ar–*H*), 6.65 (*s*, 1H, Ar–*H*), 6.81 (*s*, 1H, C_5-H), 7.35 (*bs*, 5H, $O-CH_2-C_6H_5$); MS: *m/z* 417 (M^+), 402 (M^+-15), 360 (M^+-57), 326 (M^+-91), 298 ($M^+-91-28$), 283, 269, 91.

(±)-*O-Benzylisosalutaridine* (**23**): yield 12.6%; base methiodide, m.p. 225-26° (d) (lit[9] m.p. 224-25°) and identical in all respects (co-TLC, IR, PMR and mass) with an authentic sample.

Pschorr cyclisation of **16**

16 was subjected to Pschorr cyclisation[9] as described in the case of **17** to give (±)-*O-benzyl-N-methyllaurotetanine* (**19**) (yield 10%); base picrate, m.p. 207-08° (lit[9] m.p. 209°): (±)-*O-benzylisosalutaridine* (**23**) (yield 12.6%); base methiodide, m.p. 223-24° (d) (lit[9] m.p. 224-25°); (±)-*O-benzyllaudanine* (**21**) (yield 14%); base picrate, m.p. 152-53° (lit[9] m.p. 153-54°).

(±)-*Isoboldine* (**22**)

A mixture containing **18** (150 mg), EtOH (1 ml) and 12 *N* HCl (1 ml) was refluxed for 3 hr. The solvent and the excess of reagent were removed *in vacuo*, water (2 ml) added and basified with 28% NH_3 solution. The product was extracted with EtOAc, washed with water, dried (anhyd. Na_2SO_4) and the solvent removed to afford **22**, yield 60 mg (66%), m.p. 205-6° (d) (ether-hexane) (lit.[10] m.p. 208-9° (d).

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Phase Transfer Catalysed Alkylations of Bis(benzenesulfonyl)methane

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Alkylations of bis(benzenesulfonyl)methane under phase transfer catalysed conditions are reported. Variations in the phase transfer catalyst, alkylating reagent and the cosolvent have been studied with a view to understanding the course of the reaction. Optimum conditions for effecting mono- or dialkylation have been established.

The last decade has witnessed an increased interest in the chemistry of the sulfone group[1]. Because of the ease with which the sulfone group can be transformed into other functional groups under a variety of conditions, it occupies a unique position in organic synthesis[1]. However, geminal disulfones have attracted very little attention and only recently these have been used for cycloalkylation[2], macrolide formation[3] and as a 1,3-dipole synthon[4]. Results from this laboratory have shown that 1,1-bis (benzenesulfonyl)ethene, a geminal disulfone olefin can be used in Michael[5] and Diels-Alder reactions[6] and this has been complemented by the results from other laboratories[7-9].

In synthetic organic chemistry C–C bond formation is pre-eminent, and new methods are being continually sought to achieve this particular goal. One such strategy of recent origin is alkylation under phase transfer catalysed (PTC) conditions. The ease with which PTC alkylations can be performed on activated substrates and the absence of any such work on geminal disulfones attracted our attention and accordingly alkylation of bis(benzenesulfonyl)methane (**1**) with a variety of alkylating agents under PTC conditions was studied. The recent reports of Trost[10] and Genet[11] have prompted us to reveal our findings in this area and the results obtained form the basis of the present paper.

As a representative example, *n*-hexyl bromide was chosen as the alkylating reagent and its reaction with **1** using different PT catalysts was studied in a single phase (50% aq. NaOH). Using one equivalent of *n*-hexyl bromide and tetra-*n*-butylammonium bromide (TBAB) as a PT catalysts, the monoalkylated product 1,1-bis(benzenesulfonyl)heptane (**2**) was obtained in 73% yield. In an effort to improve the yield the reaction was repeated using two equivalents of *n*-hexyl bromide. Gratifyingly, the yield of **2** went upto 95% (Table 1). Subsequently, all alkylation reactions were carried out using two equivalents of the alkylating reagent unless mentioned otherwise. Table 1 gives the results using other PT catalysts for the alkylation of **1** with *n*-hexyl bromide. Employing a two-phase system of 50% aq. sodium hydroxide and dichloromethane as cosolvent did not improve the yields in entries 4-7 in Table 1. As the yields were satisfactory in entries 1-3, these reactions were not carried out using two-phase conditions.

Table 1—Alkylation of **1** with *n*-Hexyl Bromide using Different PT Catalysts

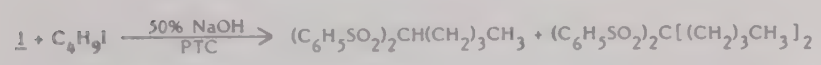
$(C_6H_5SO_2)_2CH_2$ (**1**) + *n*-$C_6H_{13}Br$ $\xrightarrow[PTC]{50\%\ NaOH}$ $(C_6H_5SO_2)_2CH$-$(CH_2)_5CH_3$ (**2**)

	PT catalyst	Yield (%) of **2**
1	Tetra-*n*-butylammonium bromide (TBAB)	95 (73)
2	Tetra-*n*-butylammonium hydrogen sulphate (TBAHS)	75
3	Tricaprylmethylammonium chloride (TCMAC)	70
4	Cetylpyridinum chloride (CPC)	28
5	Cetyltrimethylammonium bromide (CTMAB)	21
6	Benzyltriethylammonium chloride (BTEAC)	20
7	18-Crown-6	22

The effect of the leaving group of the alkylating reagent on the reaction is an aspect which has not received much attention in PTC alkylations. Therefore, alkylations of **1** with *n*-butyl chloride, bromide and iodide in a single phase (50% aq. NaOH) employing TBAB as PT catalyst were then carried out. While the reaction of **1** with 2 equivalents of *n*-butyl chloride did not proceed at all, *n*-butyl bromide under similar conditions gave an 85% yield of the monoalkylated product, 1,1-bis(benzenesulfonyl)-pentane (**3**)[12]. Finally, with 2 equivalents of *n*-butyl iodide, the dialkylated product of **1**, viz. 5,5-bis(benzenesulfonyl)nonane (**4**)[12] was obtained in 75% yield along with 11% of monoalkylated product **3**. However, when only 1 equivalent of *n*-butyl iodide was used, a mixture of **3** and **4** (61% and 10%, respectively)

was obtained. The reaction of **1** with *n*-butyl iodide in the presence of different PT catalysts led to only **3** with CPC, CTMAB and BTEAC and to a mixture of **3** and **4** with TBAHS and TCMAC. With TBAHS and TCMAC only **3** was obtained when one equivalent of *n*-butyl iodide was used (Table 2). The results in Table 2 indicate that the course of the reaction (mono or dialkylation) can probably be controlled by the appropriate choice of the alkylating reagent and/or the PT catalyst.

Table 2—Alkylation of **1** with *n*-Butyl Iodide in the Presence of Different PT Catalysts



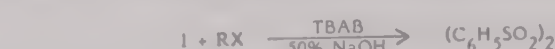
PT catalyst	Yield (%) of **3**	**4**
1 TBAB	11(61)	75(10)*
2 TBAHS	21(91)	54
3 TCMAC	20(83)	59
4 CPC	57	—
5 CTMAB	62	—
6 BTEAC	63	—

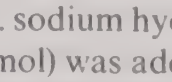
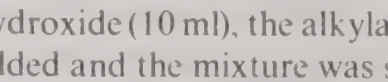
*Yield when only one equivalent of *n*-butyl iodide is used.

Attention was then focused on studying the reaction of **1** with *n*-butyl bromide and iodide in a two-phase system with dichloromethane and toluene as cosolvents and TBAB as the PT catalyst. Under these experimental conditions only the monoalkylated product (**3**) was obtained. The use of toluene as cosolvent and *n*-butyl bromide as alkylating reagent led to rather poor yield (45%) of **3**. The yield of **3** in this reaction in the presence of dichloromethane was better (57%). With *n*-butyl iodide the yields of **3** were 85% and 77% in dichloromethane and toluene as cosolvents respectively. Hence, further study of the alkylation reaction using different PT catalysts was limited to *n*-butyl iodide and dichloromethane. The other PT catalysts showed a behaviour similar to that of TBAB in effecting monoalkylation of **1** to give **3**. However, the yields of **3** in the presence of CPC, CTMAB and BTEAC were 45, 62 and 57%, respectively. It is of interest to note that whereas the reaction of **1** with *n*-butyl iodide in a one-phase system gave either the dialkylated product **4** or the monoalkylated product **3** depending upon the reaction conditions, in a two-phase system, the same reaction always gave only **3**. The reason for this difference in reactivity is not yet clear.

The results presented above indicate that the best conditions for the PTC alkylation of **1** would be the use

Table 3—Alkylation of **1** with Different Alkylating Agents



RX	Product	Yield (%)
CH_3I	5 R,R′ = $-CH_3$	100 (ref. 12)
CH_3CH_2Br	6 R,R′ = $-CH_2CH_3$	100
$CH_2=CHCH_2Br$	7 R,R′ = $-CH_2-CH=CH_2$	90
$Br(CH_2)_2Br$	8 R,R′ = $-(CH_2)_2-$	90 (ref. 13)
$Br(CH_2)_3Br$	9 R,R′ = $-(CH_2)_3-$	90
$Br(CH_2)_4Br$	10 R,R′ = $-(CH_2)_4-$	100
$Br(CH_2)_5Br$	11 R,R′ = $-(CH_2)_5-$	80
$Br(CH_2)_6Br$	12 R,R′ = $-(CH_2)_6-$	75
$C_6H_5CH_2Br$	13 R = $-CH_2C_6H_5$, R′ = H	78
$CH_3(CH_2)_2Br$	14 R = $-(CH_2)_2CH_3$, R′ = H	100
	15 R =  , R′ = H	100

of TBAB as the catalyst and 50% aq. sodium hydroxide as the medium. A large number of alkylation reactions were successfully performed under these conditions and the results are given in Table 3. It is seen from Table 3 that α,ω-dibromides all undergo cyclization on reaction with **1**. Incidentally, this is the most convenient method for the preparation of 1,1-bis(benzenesulfonyl)cyclopropane (**8**), a compound which has been used as a 1,3-dipole synthon[4].

Since desulfonylation (either mono[3] or di[1,5]) can be effectively carried out in a stepwise fashion, we believe that PTC catalysed alkylation of **1** could be a very useful reaction in arriving at natural products of long chain hydrocarbon, pheromones. Further studies in utilizing this mild reaction are in progress.

Experimental Procedure

Infrared spectra were recorded in KBr on a Perkin-Elmer 297 spectrophotometer and PMR spectra in $CDCl_3$ on a JEOL MH100 instrument using TMS as an internal standard. Melting points were determined with a Buchi SMP-20 apparatus and are uncorrected. All the alkylating reagents used were distilled prior to use.

General procedure for alkylations in one-phase system

To a mixture of **1** (1 mmol) and PTC (1 mmol) in 50% aq. sodium hydroxide (10 ml), the alkylating reagent (2 mmol) was added and the mixture was stirred for 3 hr at 25-30°C. The reaction mixture was made sacidic (*p*H 2-3), extracted with dichloromethane and the organic extract washed with water, dried ($MgSO_4$) and evaporated to give the product.

General procedure for alkylations in two-phase system

To a mixture of **1** (1 mmol) and PTC (1 mmol) in 50%

Table 4—Physical and Spectral Data of Compounds **2-15** Synthesized

Product	m.p. (°C)	IR (cm^{-1})	^{1}HNMR (δ)	MS (m/z)
2	80-81 (Isopropanol-Ethanol)	2950, 1320, 1160	8.0-7.52 (*m*, 10H), 4.4-4.32 (*t*, 1H), 2.24-1.08 (*bm*, 10H), 0.92-0.8 (*t*, 3H)	239 (M-141)
6	166 (Ethanol)	3050, 1320, 1160	8.24-7.52 (*m*, 10H), 2.48-2.24 (*q*, 4H), 1.32-1.2 (*t*, 6H)	352 (M^+)
7	95 (Ethanol)	3100, 1650, 1310, 1150	8.16-7.52 (*m*, 10H), 6.2-5.84 (*m*, 2H), 5.28-5.12 (*m*, 4H), 3.04-2.96 (*d*, 4H)	376 (M^+)
9	117-18 (Benzene-Hexane)	3000, 1600, 1320, 1150	8.0-7.4 (*m*, 10H), 3.0-2.8 (*t*, 4H), 2.2-2.0 (*m*, 2H)	195 (M-141)
10	141-42 (Benzene-Hexane)	3000, 1450, 1310, 1140	8.0-7.4 (*m*, 10H), 2.52-2.4 (*m*, 4H), 1.76-1.6 (*m*, 4H)	350 (M^+)
11	158 (Methanol)	2900, 1320, 1160	7.72-7.2 (*m*, 10H), 2.2-2.12 (*m*, 4H), 2.0-1.8 (*m*, 4H), 1.48-1.4 (*m*, 2H)	364 (M^+)
12	174 (Isopropanol)	2950, 1310, 1140	8.04-7.52 (*m*, 10H), 2.36-2.24 (*m*, 4H), 2.04-1.8 (*m*, 4H), 1.68-1.44 (*m*, 4H)	237 (M-141)
13	135 (Ethanol)	3100, 1600, 1320, 1150	8.0-7.56 (*m*, 10H), 7.2 (*s*, 5H), 4.8-4.68 (*t*, 1H), 4.52-4.48 (*d*, 2H)	245 (M-141)
14	128 (Methanol-Isopropanol)	2950, 1310, 1140	7.92-7.48 (*m*, 10H), 4.36-4.28 (*t*, 1H), 2.2-2.0 (*m*, 2H), 1.68-1.40 (*m*, 2H), 0.88-0.72 (*t*, 3H)	338 (M^+)
15	140-41 (Methanol)	2950, 1320, 1160	7.88-7.28 (*m*, 10H), 4.6-4.48 (*t*, 1H), 4.2-4.12 (*t*, 1H), 3.6-2.96 (*m*, 6H), 1.68-1.4 (*m*, 2H), 1.32-1.10 (*m*, 2H)	410 (M^+)

aq. sodium hydroxide (10 ml) and dichloromethane (10 ml), the alkylating reagent (2 mmol) was added and allowed to stir at 25-30°C for 3 hr. After acidification, the organic layer was separated, washed with water, dried ($MgSO_4$) and evaporated to give the corresponding alkylated product.

In cases where a mixture of mono and dialkylated products was obtained, they were separated using column chromatography (silica gel) employing hexane and ethyl acetate as eluents.

The spectral data of all the products are given in Table 4. All new products gave satisfactory microanalytical data (C,H).

Acknowledgement

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Organic Synthesis under PTC: Part 6—Preparation & Decomposition of Chiral Phase Transfer Catalysts Derived from Quinine

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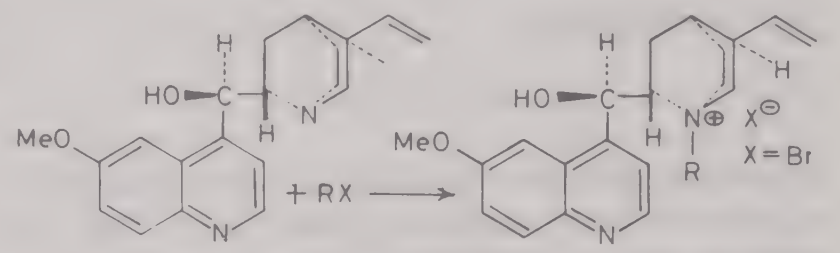
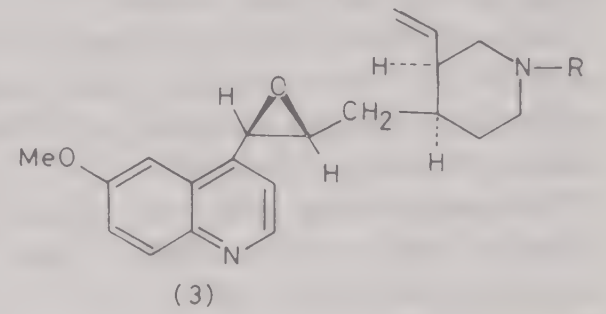
Alkyl aryl quininium salts (**2a-d**) have been prepared from quinine (**1**) and appropriate organic halides and their decomposition under phase transfer (PT) conditions using different concentrations of aqueous sodium hydroxide as base has been investigated. The products isolated have been characterized as the corresponding oxirane derivatives (**3a-d**) by IR, PMR and mass data.

Asymmetric induction under phase transfer conditions (PTC) has been reported in a variety of reactions, viz. epoxidation[1-3], sodium borohydride reduction[4-6], nucleophilic substitutions[7-8], alkylations[9-10] and Micheal addition[11-13] reactions. In all these reactions optically active catalysts derived from Cinchona or Ephedra alkaloids have been used. All these catalysts invariably possess a $\beta-OH$ group which has been considered to be essential for asymmetric induction. But under the reaction conditions these catalysts are known to decompose[14]. In addition to the presence of $\beta-OH$ group the enantiomeric excess (e.e) in these reactions has been found to depend upon two other factors: (i) rigidity of the structure of the catalyst; and (ii) the chain length of the alkyl/aryl halide used for the preparation of onium salts. Presently we have investigated the effect of the chain length on the stability of the catalyst under the reaction conditions using different concentrations of aqueous sodium hydroxide at different temperatures.



(1) (2)

(3)
a, R = C_4H_9
b, R = C_6H_{13}
c, R = C_8H_{17}
d, R = NO_2 CH_2-



(3)

A mixture of N-butylquininium bromide (**2**, R = *n*-Bu), benzene and 50% sodium hydroxide when stirred at room temperature afforded a product (R_f = 0.3, 15:1, $CHCl_3$ – MeOH) in 40% yield; $[\alpha]_D^{20} - 101.85°$ (*c*, 0.108, $CHCl_3$). Its mass spectrum exhibited the parent ion peak at *m/z* 379. Its PMR spectrum displayed signals at δ 1.0-3.1 (*m*, 20H, *n*-Bu and piperidyl and C_3-CH_2), 3.9 (*s*, 3H, $-OCH_3$), 4.1 (*d*, *J* = 2 Hz, 1H, oxirane H adjacent to quinolyl ring), 7.2-8.8 (*m*, aromatic, 5H). On the basis of these spectral data it has been assigned the structure as *trans*-2(*R*)-6-methoxy-4-quinolyl-3-(1-*n*-butyl-3(*R*)-vinyl-4-*cis*-piperidyl)methyl oxirane (**3**, R = *n*-butyl). This structure assignment was further corroborated by the appearance of Bohlmann bands in its IR spectrum due to oxirane ring system (C – H) at 2795 and 2745 cm^{-1}.

In order to study the effect of concentration of aqueous sodium hydroxide and temperature on the stability of this catalyst, the above reaction was carried out in the presence of varying concentrations of aqueous sodium hydroxide (50%, 30%, 10%) at different temperatures (room temperature and 150°). In all these cases the epoxide was formed and the results of these investigations are presented in Table 1.

However, on using 0.6 *M* $NaBH_4$ solution at room temperature no decomposition of the salt was noticed (TLC), indicating that chiral PT catalyst when used in $NaBH_4$ reduction at room temperature was quite stable.

In order to investigate the effect of chain length on the stability of the catalyst, different quininium salts (**2**, R = *n*-hexyl, *n*-octyl and *p*-nitrobenzyl) were prepared and their decomposition was studied under the same reaction conditions as for **2** (R = *n*-Bu). The results of these investigations are also presented in Table 1.

The results presented in Table 1 show that the decomposition of quininium salts depends upon (i) concentration of the base, (ii) reaction temperature and

Table 1—Decomposition of Various Quininium Bromides (2) at Varying Concentrations of aq NaOH and Different Temperature

Quininium bromide	Conditions	Temp. (°C)	Time (hr)	Decomposition (%)
n-Butyl	50% NaOH	RT	3	40
		150	2	50
	30% NaOH	RT	3	15
		150	2	30
	10% NaOH	RT	3	5
		150	2	30
	0.6*M* $NaBH_4$	RT	1	0
n-Hexyl	50% NaOH	RT	3	30
		150	3	40
	30% NaOH	RT	3	10
		150	2	15
	10% NaOH	RT	3	5
		150	3	15
	0.6*M* $NaBH_4$	RT	1	0
n-Octyl	50% NaOH	RT	3	20
		150	4	30
	30% NaOH	RT	3	10
		150	1	20
	10% NaOH	RT	3	5
		150	2	10
	0.6*M* $NaBH_4$	RT	1	0
p-Nitro-benzyl	50% NaOH	RT	3	10
		150	3	20
	30% NaOH	RT	3	5
		150	3	15
	10% NaOH	RT	6	5
		150	3	5
	0.6*M* $NaBH_4$	RT	1	0

(iii) the chain length of the N-substituent. As the concentration of the base and the reaction temperature are increased the rates of decomposition of salts and hence the rates of formation of oxirane ring system increase. However, increase in the chain length of N-substituent decreases the rate of decomposition of the quininium salt. For instance in 50% aq sodium hydroxide at room temperature after three hours the decomposition is 40%, 40%, 20% and 10% for N-butyl, N-hexyl, N-octyl and N-*p*-nitrobenzyl substituents respectively.

The mass spectra of the oxirane ring systems (**3a-d**) show some characteristic peaks which further corroborate the structure assignments (see Table 2 also). In the mass spectra of **3a-d**, the parent ion peaks are very weak and in the case of **3d** it is not visible at all; however a peak at $M^+ - NO_2$ is very significant. All the compounds (**3a-d**) exhibit a peak at *m/z* 337 due to the ion (**5**) formed from the parent ion by the loss of R (Scheme 1). The other daughter ions originate from the ion (**5**) through different modes of decomposition of the epoxide (Scheme 1). The epoxide via α-cleavage and simultaneous transfer of a γ-hydrogen forms a peak at

Table 2—Intensity of Various Ions in Mass Spectrum Relative to Base Ion

	Relative abundance (%) when R =			
Ion	Butyl	Hexyl	Octyl	*p*-Nitro
5	97.5	100.0	69.76	34.88
6	83.72	13.95	100	90.69
7	100.00	4.651	97.5	100.00
8	5.00	2.325	10.00	2.32
9	5.000	4.762	5.263	2.381
10	10.00	13.95	12.5	6.97
11	7.50	2.32	12.50	4.65

m/z 43 (ion **6**) and when the cleavage of β-bond occurs followed by transfer of γ-hydrogen a peak at *m/z* 57 (ion **7**) appears. The other modes of formation of ions is via the ring-opening of epoxide. For ring-opening there are two possible pathways (Scheme 2); path (a) gives a significant peak at *m/z* 172; while path (b) forms an ion at *m/z* 165.

Experimental Procedure

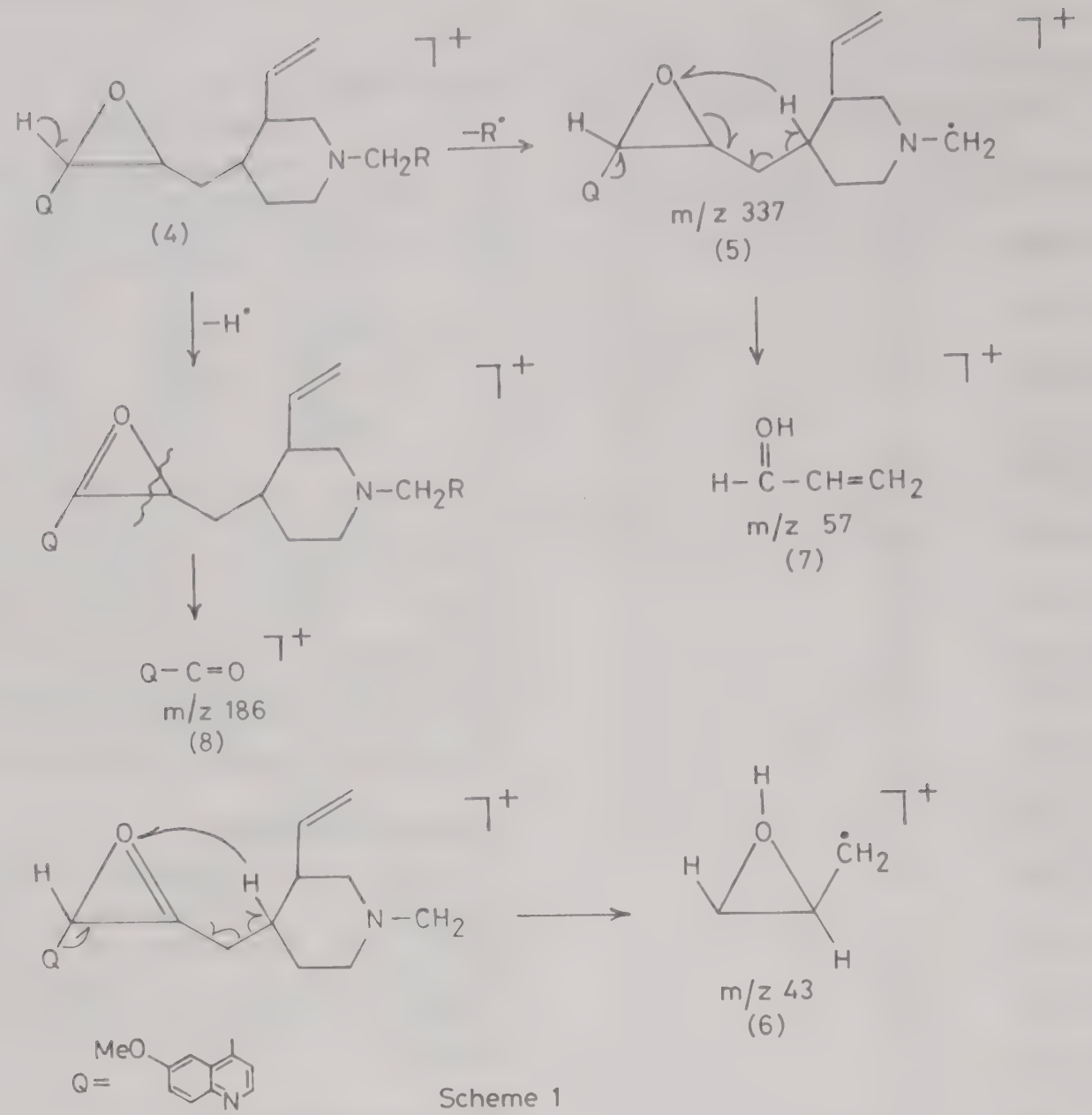
IR spectra were recorded on Spectromom 2000 spectrophotometer, PMR spectra on a Jeol 90 MHz instrument and mass spectra on a Hitachi/Perkin-Elmer RMU-60D instrument. Optical rotations were measured using a Hilger standard polarimeter (Watts Microptic).

Preparation of quininium salts:
General procedure

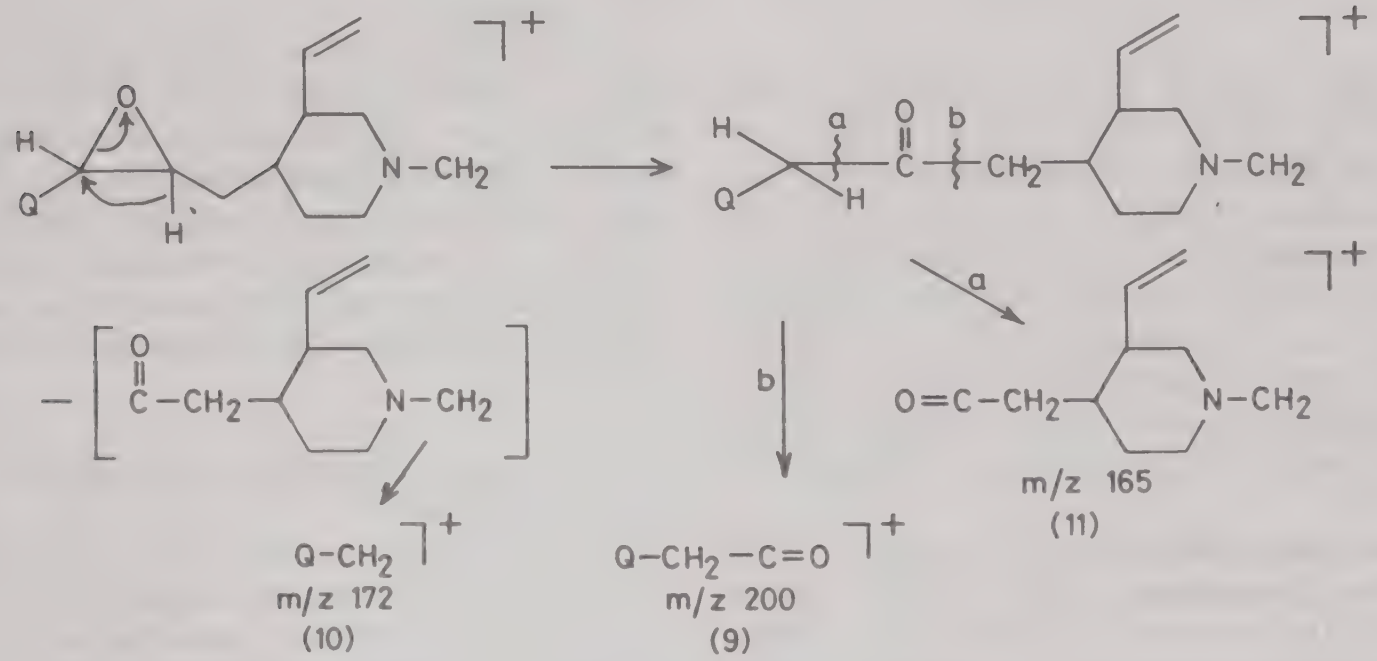
To a solution of quinine (**1**, 10 mmol) in benzene (10 ml) and ethanol (2 ml) was added appropriate alkyl halide (10 mmol). The reaction mixture was allowed to stand at room temperature for 26 hr, concentrated under diminished pressure and the residue thus obtained was washed with *n*-hexane to give the corresponding optically active quaternary quininium salts (**2a-d**). These were recrystallised from ethanol-ether mixture.

Decomposition of optically active salts (**2a-d**):
General procedure

To a solution of quininium salt (**2**, 1 g) in benzene was added sodium hydroxide solution (50%, 10 ml) and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture washed with water and the product was isolated through column chromatography using benzene-ethyl acetate mixture (70:30). Similar experiments were performed using 30%, 10% sodium hydroxide solution and 0.6 *M* $NaBH_4$ solution respectively and the results obtained are given in Table 1. The following epoxides (**3a-d**) were isolated and characterised.



Scheme 1



Scheme 2

Epoxide (**3a**): Oily product; M^+ 379; $[\alpha]_D^{20}$ – 101.85 (*c*, 0.108, $CHCl_3$); PMR($CDCl_3$): δ 1.0-3.1 (*m*, *n*-Bu, and piperidyl and C_3-CH_2), 3.9 (*s*, 3H, $-OCH_3$), 4.1 (*d*, $J = 2$ Hz, 1H oxirane adjacent to quinolyl ring), 7.2-8.8 (*m*, aromatic H); IR($CHCl_3$): 3020, 2990, 2800, 2795, 2745, 1605, 1120 cm^{-1}.

Epoxide (**3b**): Oily product; M^+ 407 $[\alpha]_D^{20}$ – 74.2 (*c*, 0.256, $CHCl_3$); PMR($CDCl_3$): δ 0.8-3.1 (*m*, *n*-hexyl and piperidyl and C_3-CH_2), 3.95 (*s*, 3H, $-OCH_3$), 4.1 (*d*, 1H, oxirane adjacent to quinolyl ring); 7.3-8.8 (*m*, aromatic H); IR($CHCl_3$): 3000, 2900, 2880, 2800, 2795, 2745, 1600, 1450, 1190 cm^{-1}.

Epoxide (**3c**): Oily product; M^+ 435; $[\alpha]_D^{20} -68.9°$ (*c*, 0.232, $CHCl_3$); PMR($CDCl_3$): δ 1.2-3.1 (*m*, *n*-octyl and piperidyl and C_3-CH_2), 3.95 (*s*, $-OCH_3$), 4.15 (*d*, 1H, oxirane adjacent to quinolyl ring), 7.3-8.7 (*m*, aromatic H); IR($CHCl_3$): 2990, 2795, 2750, 2715, 1630, 1510, 1470, 1370, 1210, 1130 cm^{-1}.

Epoxide (**3d**): Oily product; $M^+ - NO_2$ 419; $[\alpha]_D^{20}$ $-90.9°$ (*c*, 0.044, $CHCl_3$); PMR($CDCl_3$): δ 1.15-3.1 (*m*, $-NCH_2$ and piperidyl and C_3-CH_2), 3.95 (*s*, $-OCH_3$), 4.15 (*d*, 1H, oxirane adjacent to quinolyl ring), 7.2-8.8 (*m*, aromatic H); IR($CHCl_3$): 2900, 2785, 2745, 1605, 1505, 1350, 1120 cm^{-1}.

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Synthesis of Carbazoles via Diels-Alder Reaction of 3-Vinylindoles

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Diels-Alder reaction of 3-(β-nitrovinyl)indole (**1**) with acrylonitrile, ethyl acrylate and cinnamaldehyde gives the carbazoles **4**, **5** and **6** respectively by the loss of nitro group and aromatization. The reaction of 3-(β-nitro-β-methylvinyl)indole (**2**) with acrylonitrile and ethyl acrylate gives the carbazoles **7** and **8** respectively. Diels-Alder reaction of 3-(β-carbethoxyvinyl)indole (**3**) with acrylonitrile and ethyl acrylate gives the tetrahydrocarbazoles **10** and **12** (at lower temperature) and carbazoles **9** and **11** (at higher temperature), respectively.

Carbazole system is present in many naturally occurring alkaloids[1], and many synthetic methods are reported for this system[1]. In earlier papers[2,3] from our laboratory the synthesis of carbazole skeleton involving Diels-Alder reaction on 2-vinylindoles was reported. In literature there are reports of the *in situ* synthesis of 3-vinylindoles and their use for the synthesis of carbazoles[4]. Presently a new route to carbazole skeleton has been developed using Diels-Alder reaction on 3-vinylindoles.

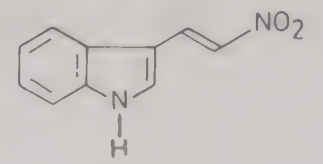
For the present study three 3-vinylindoles (**1-3**) were selected as dienes. Compounds **1** and **2** were obtained by the condensation of 3-formylindole with nitromethane[5] and nitroethane[6] respectively, in the presence of ammonium acetate, while **3** was obtained by the condensation of 3-formylindole with carbethoxymethylenetriphenylphosphorane.

The dienophiles chosen were acrylonitrile, ethyl acrylate and cinnamaldehyde.

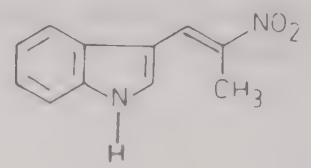
Diels-Alder reaction of **1** with acrylonitrile gave a solid ($C_{13}H_8N_2$), which was characterised as **4** on the basis of its IR and PMR spectral data (see Tables 1 and 2). The presence of only aromatic protons and the absence of other protons in its PMR spectrum (Table 2) obviouslv indicated that aromatization had occurred during Diels-Alder reaction. Such aromatization, by the loss of a nitro group present in the diene, during Diels-Alder reaction has been reported[7].

The three low field aromatic protons at δ 7.65 (*dd*, J = 7 and 1 Hz), 8.05 (*dd*, J = 7 and 1 Hz) and 8.22 (*dd*, J = 8 and 1 Hz) could be assigned to C_2-H, C_5-H and C_4-H respectively. This required the $-CN$ group to be placed at C-1 (as in **4**) and not at C-2 (as in **4a**). In agreement with structure **4** all the three low field protons at C-2, C-5 and C-4 respectively all showed the presence of one *ortho* and one *meta* neighbour.

Reaction of **1** with ethyl acrylate gave **5** the structure of which was confirmed by the presence of a deshielded, three-proton multiplet in the PMR spectrum.



1



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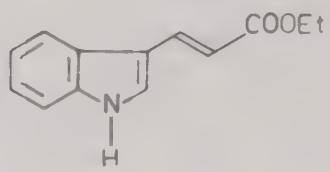

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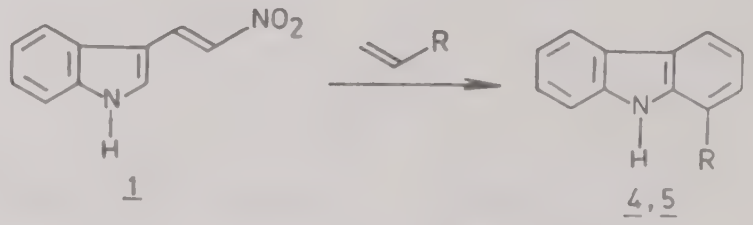
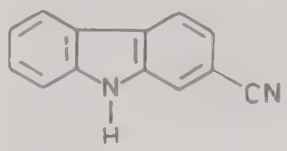


1 → 4,5

4 R=-CN
5 R=-COOEt



4a

Reaction of **1** with cinnamaldehyde gave **6** ($C_{19}H_{13}NO$) which in its PMR spectrum displayed a eight-proton multiplet at δ 7.1-7.65 and a most deshielded aromatic proton at δ 8.35 as a doublet (Table 2). Structure of the above compound was confirmed by spin decoupling experiment. When signal at δ 7.22 was irradiated the doublet at δ 8.35 became a singlet, showing the loss of *ortho* coupling of 7 Hz. Thus these two signals (δ 7.22 and 8.35) were due to two mutually *ortho*-coupled protons. Since the C_4-H of carbazoles are known to be deshielded, these

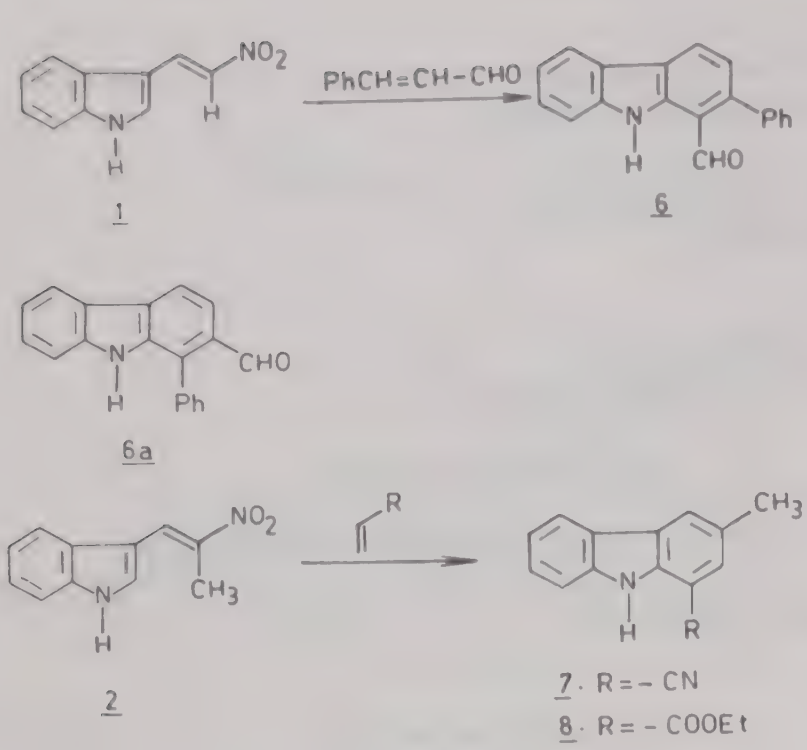
Table 1—Characterisation Data of Carbazoles (**4-9,11**) and Tetrahydrocarbazoles (**10,12**) Obtained from Diels-Alder Reactions of **1**, **2** and **3** with Various Dienophiles

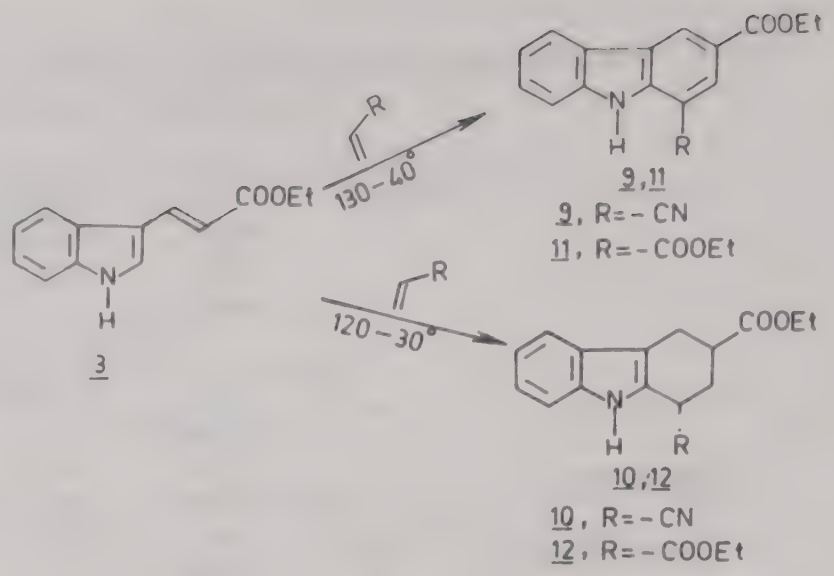
Dienophile	Product*	Reaction period, (hr) (temp, °C)	m.p. (lit. m.p.) (°C)	Yield (%)	IR (nujol)/cm $^{-1}$
		Diene: 3-(β-Nitrovinyl)indole (**1**)			
Acrylonitrile	**4**	25 (130-40)	188-89	39	3300 (>NH), 2250 (−CN)
Ethyl acrylate	**5**	25 (130-40)	103 (105)[9]	40	3390 (>NH), 1690 (ester CO)
Cinnamaldehyde	**6**	21 (130-40)	228	21	3300-3400 (*bb* of (>NH), 1670 (aldehyde CO)
		Diene: 3-(β-Nitro-β-methylvinyl)indole (**2**)			
Acrylonitrile	**7**	25 (130-40)	192	33	3300 (>NH), 2250 (−CN)
Ethyl acrylate	**8**	24 (130-40)	108-9	14	3350 (>NH), 1680 (ester CO)
		Diene: 3-(β-Carbethoxyvinyl)indole (**3**)			
Acrylonitrile	**9**	25 (130-40)	187-90	28	3290 (>NH), 2250 (−CN), 1750 (ester CO)
Acrylonitrile	**10**	24 (120-30)	124-28	13	3300 (>NH), 2250 (−CN), 1720 (ester CO)
Ethylacrylate	**11**	25 (130-40)	180-81	23	3300 (>NH), 1690 (ester CO)
Ethylacrylate	**12**	24 (120-30)	78-79	17	3310 (>NH), 1650 (ester CO)

*All the products gave satisfactory elemental analyses (C, ±0.33%; H, ±0.2%).

Table 2—PMR Data of Carbazoles (**4-9,11**) and Tetrahydrocarbazoles (**10,12**) Obtained from Diels-Alder Reaction of **1**,**2** and **3** with Various Dienophiles

Carbazole/ Tetrahydro-carbazole	PMR (δ scale)
4[10]	7.15-7.55 (*m*, 4H, aromatic), 7.65 (*dd*, $J=7$ & 1 Hz, 1H, C_2-H), 8.05 (*d*, $J=7$ Hz, 1H, C_5-H changed to a *dd*, $J=7$ & 1 Hz, after adding 2-3 drops of DMSO-d_6), 8.22 (*d*, $J=8$ Hz, 1H, C_4-H, changed to a *dd*, $J=8$ & 1 Hz after adding 2-3 drops of DMSO-d_6), 8.65-8.95 (*bs*, 1H, >N−H)
5	1.42 (*t*, $J=7$ Hz, 3H, $-COOCH_2CH_3$), 4.45 (*q*, $J=7$ Hz, 2H, $-COOCH_2CH_3$), 7.0-7.5 (*m*, 4H, aromatic), 7.9-8.25 (*m*, 3H, C_2-H, C_4-H, C_5-H), 9.7-10.05 (*bs*, 1H, >N−H).
6	7.1-7.65 (*m*, 8H, aromatic), 7.75 (*dd*, $J=9$ & 1 Hz, 1H, aromatic), 8.12 (*d*, $J=8$ Hz, 1H, C_5-H), 8.35 (*d*, $J=7$ Hz, 1H, C_4-H), 10.02 (*s*, 1H, Ar−CHO).
7	2.52 (*s*, 3H, $Ar-CH_3$), 7.1-7.7 (*m*, 4H, aromatic), 7.9-8.15 (*m*, 2H, C_4-H and C_5-H), 11.1-11.4 (*bs*, 1H, >N−H).
8	1.5 (*t*, $J=7$ Hz, 3H, $-COOCH_2CH_3$), 2.59 (*s*, 3H, $Ar-CH_3$), 4.5 (*q*, $J=7$ Hz, 2H, $-COOCH_2CH_3$), 7.1-7.6 (*m*, 3H, aromatic), 7.89 (*d*, $J=1$ Hz, 1H, C_4-H or C_2-H), 8.00 (*d*, $J=7$ Hz, 1H, C_5-H), 8.05 (*d*, $J=1$ Hz, 1H, C_4-H or C_2-H), 8.00 (*d*, $J=7$ Hz, 1H, C_5-H), 8.05 (*d*, $J=1$ Hz, 1H, C_2-H or C_4-H), 9.6-9.9 (*bs*, 1H, >N−H).
9	1.45 (*t*, $J=7$ Hz, 3H, $-COOCH_2CH_3$), 4.48 (*q*, $J=7$ Hz, 2H, $-COOCH_2CH_3$), 7.2-7.6 (*m*, 3H, aromatic), 8.1 (*dd*, $J=8$ & 1 Hz, 1H, C_5-H), 8.39 (*d*, $J=2$ Hz, 1H, C_2-H). 8.9 (*d*, $J=2$ Hz, 1H, C_4-H), 9.2-9.45 (*bs*, 1H, >N−H).
10	1.3 (*t*, $J=6$ Hz, 3H, $-COOCH_2CH_3$), 1.32 (*t*, $J=7$ Hz, 3H, $-COOCH_2CH_3$), 1.6-1.9 (*m*, 1H, alicylic), 2.1-2.55 (*m*, 3H, alicylic), 2.6-3.15 (*m*, 6H, alicyclic), 3.95-4.4 (*m*, 6H, 2× $-COOCH_2CH_3$ + two alicyclic), 6.95-7.55 (*m*, 2×4H, aromatic), 8.2-8.5 (2×*bs*, 2H, 2×>N−H).
11[11]	1.45 (*t*, $J=7$ Hz, 3H, $-COOCH_2CH_3$), 1.48 (*t*, $J=7$ Hz, 3H, $-COOCH_2CH_3$), 4.45 (*q*, $J=7$ Hz, 2H, $-COOCH_2CH_3$), 4.5 (*q*, $J=7$ Hz, 2H, $-COOCH_2CH_3$), 7.2-7.6 (*m*, 3H, aromatic), 8.12 (*dd*, $J=8$ & 1 Hz, 1H, C_5-H), 8.75 (*d*, $J=1$ Hz, 1H, C_2-H), 8.9 (*d*, $J=1$ Hz, 1H, C_4-H), 10.0-10.25 (*bs*, 1H, >N−H).
12	1.35 (*t*, $J=7$ Hz, 2×3H, 2× $-COOCH_2CH_3$), 2.05-2.4 (*m*, 1H, alicylic), 2.5-3.25 (*m*, 4H, alicylic), 3.75-4.05 (*m*, 1H, alicylic), 4.25 (2×*q*, $J=7$ Hz, 4H, 2× $-COOCH_2CH_3$), 6.95-7.5 (*m*, 4H, aromatic), 8.4-8.7 (*bs*, 1H, >N−H).





signals were assigned to C_3-H and C_4-H respectively. The deshielding of C_3-H arises by the proximity of formyl group, thus suggesting structure **6** and ruling out structure **6a**.

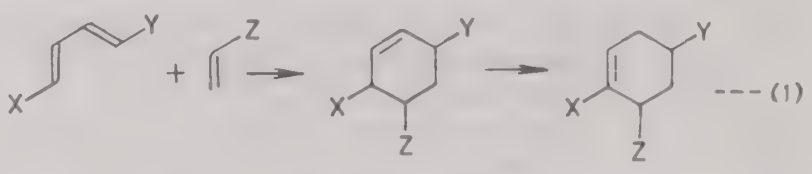
Reaction of **2** with acrylonitrile led to **7** as a white solid ($C_{14}H_{10}N_2$). Its IR spectrum did not show any peak due to NO_2 group and its PMR spectrum displayed no signal due to alicyclic protons. Thus as in the case **1** the $-NO_2$ group was eliminated from **2** under the reaction conditions giving an aromatized product. PMR spectrum further indicated a two-proton multiplet at δ 7.9-8.15. By irradiation of the signal at δ 8.00, *meta*-coupled doublet at δ 7.45 became a sharp singlet. Thus these two signals (δ 8.00 and 7.45) could be assigned to mutually coupled protons *meta* with respect to each other, i.e. to C_4-H and C_2-H respectively, thereby confirming structure **7** for this compound. With ethyl acrylate **2** afforded **8**, the structure of which was confirmed by IR and PMR data (Table 2).

Reaction of **3** with acrylonitrile at 130-40° led to **9** ($C_{16}H_{12}N_2O_2$) which did not show any signal due to alicyclic protons in its PMR spectrum. Thus the initial product of Diels-Alder reaction (tetrahydrocarbazole) might have aromatized during the reaction. The 1,3-relationship of cyano and carbethoxy groups was confirmed by the presence of *meta*-coupled doublets at δ 8.39 and 8.9.

To trap the intermediate tetrahydro compound (**10**) a similarly prepared reaction mixture was heated at 120-25°. Two compounds were isolated; **9** as the minor product. The major product ($C_{16}H_{16}N_2O_2$) in its PMR spectrum displayed alicyclic protons at δ 3.95-4.4 and δ 1.6-3.15 and two triplets ($J=7$ Hz) at δ 1.3 and 1.32 assigned to methyl of carbethoxy group. This suggested the above product to be a mixture of two isomers. Thus structure **10** was given to the major product. After heating at higher temperature an aromatized compound **9** was obtained thus showing that the cyano and carbethoxy groups in **10** must be in 1,3 position as in **9**.

Reaction of **3** with ethyl acrylate at 130-40° and at 120-30° gave products **11** and **12**, respectively, similar to those obtained in the above reaction.

According to molecular orbital theory an '*ortho*' adduct is obtained (i) when both diene and dienophile carry electron withdrawing groups or (ii) when a diene having a donor and dienophile having an electron withdrawing group react with each other[8]. In the case of dienes (**1-3**) an electron withdrawing group ($-NO_2$ or $-COOEt$) is present at one end and a donor ($>N-H$) at the other end. The products obtained in the present case have $>NH$ and the electron withdrawing group *ortho* to each other. Thus the dienes react with electrophiles according to Eq. (1). This suggested that



in the dienes (**1-3**) the most important substituent for deciding regioselectivity is the nitrogen atom probably due to the high electron density associated with it.

Experimental Procedure

All melting and boiling points reported are uncorrected. IR spectra were recorded on a Perkin-Elmer model 337 spectrophotometer and PMR spectra on Perkin-Elmer R-32 (90 MHz) instrument. Chemical shifts are given in δ scale using TMS as an internal standard.

3-(*β-Nitrovinyl*)*indole*[5] (**1**)

A mixture of 3-formylindole (1.74 g), ammonium acetate (0.46 g) and nitromethane (0.73 ml) in glacial

acetic acid was refluxed for 2 hr. Excess of nitromethane was removed under reduced pressure, the reaction mixture poured into ice-water to give **1** (*trans*) which recrystallized from ethanol-acetone, m.p. 169° (lit.[5] m.p. 173°); yield 33%; PMR($CDCl_3$ + DMSO-d_6): 7.05-7.38 (*m*, 2H, aromatic), 7.4-7.65 (*m*, 1H, aromatic), 7.7-8.0 (*m*, 2H, aromatic + olefinic), 8.05 (*s*, 1H, C_2-H), 8.35 (*d*, J=13 Hz, 1H, $R-CH=CH-NO_2$), 11.0-12.2 (*bs*, 1H, $>N-H$).

3-(*β-Nitro-β-methylvinyl*)*indole*[6] (**2**)

A mixture of 3-formylindole (0.5 g), ammonium acetate (0.230 g) and nitroethane (8 ml) was refluxed for 45 min at 100°. Excess of nitroethane was removed under reduced pressure. Usual work-up followed by recrystallization from ethanol-water gave **2**, m.p. 192° (lit.[6] m.p. 191-95°) in 60% yield; PMR($CDCl_3$ + DMSO-d_6): 3.1 [*s*, 3H, $R-CH=CCH_3(NO_2)$], 7.1-7.9 (*m*, 5H, aromatic), 8.5 [*s*, 1H, $R-CH=CCH_3(NO_2)$], 11.3-11.8 (*bs*, 1H, $>N-H$).

3-(*β-Carbethoxyvinyl*)*indole* (**3**)

To a solution of 3-formylindole (1 g, 0.0069 mol) in dry benzene (10-15 ml), carbethoxymethylene-triphenylphosphorane (3.6 g, 0.01 mol) was added and the reaction mixture refluxed for 4-5 hr. The solution was concentrated and the residue chromatographed over silica gel column, eluting with 25% ethyl acetate in pet. ether. From the first few fractions **3a** (*cis*) was obtained which was recrystallized from pet. ether and analysed for $C_{13}H_{13}NO_2$, m.p. 138-41°; yield 8%; PMR($CDCl_3$): 1.3 (*t*, J=7 Hz, 3H, $-COOCH_2-CH_3$), 4.22 (*q*, J=7 Hz, 2H, $-COOCH_2CH_3$), 5.75 (*d*, J=12 Hz, 1H, $RCH=CH-COOEt$), 7.00-7.55 (*m*, 4H, aromatic + one olefinic), 7.56-7.85 (*m*, 1H, aromatic), 8.8 (*d*, J=2 Hz, 1H, C_2-H), 10.5-11.0 (*bd*, 1H, $>N-H$).

The subsequent fractions gave **3** (*trans*) which was recrystallized from pet. ether and analysed for $C_{13}H_{13}NO_2$, m.p. 119°, yield 74%; PMR($CDCl_3$): 1.32 (*t*, J=7 Hz, 3H, $-COOCH_2CH_3$), 4.25 (*q*, J=7 Hz, 2H, $-COOCH_2CH_3$), 6.4 (*d*, J=16 Hz, 1H, $RCH=CH-COOEt$), 7.05-7.6 (*m*, 4H, aromatic), 7.75-8.0 (*m*, 2H, aromatic + one olefinic), 10.55-10.95 (*bs*, 1H, $>N-H$ exchangeable with D_2O).

The latter fractions gave triphenylphosphine oxide which was confirmed by m.m.p. and TLC.

Diels-Alder reaction of **1**, **2** *and* **3** *with various dienophiles*: *General procedure*:

The vinylindole (**1**, **2** or **3**) (0.001 mol) was mixed with the dienophile (in excess) in a glass tube. A pinch of hydroquinone was added and nitrogen gas was bubbled through the reaction mixture before sealing. The reaction mixture was heated at 130-40° for the periods indicated in Table 1. Removal of excess of dienophile *in vacuo* and chromatography gave **4**, **5**, **6** (from **1**), **7**, **8** (from **2**) and **9**, **11** (from **3**) and tetrahydrocarbazoles **10** and **12** (from **3**).

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Syntheses of (*Z*)-9-Hexadecen-1-yl Acetate & (*Z*)-7-Tetradecen-1-yl Acetate

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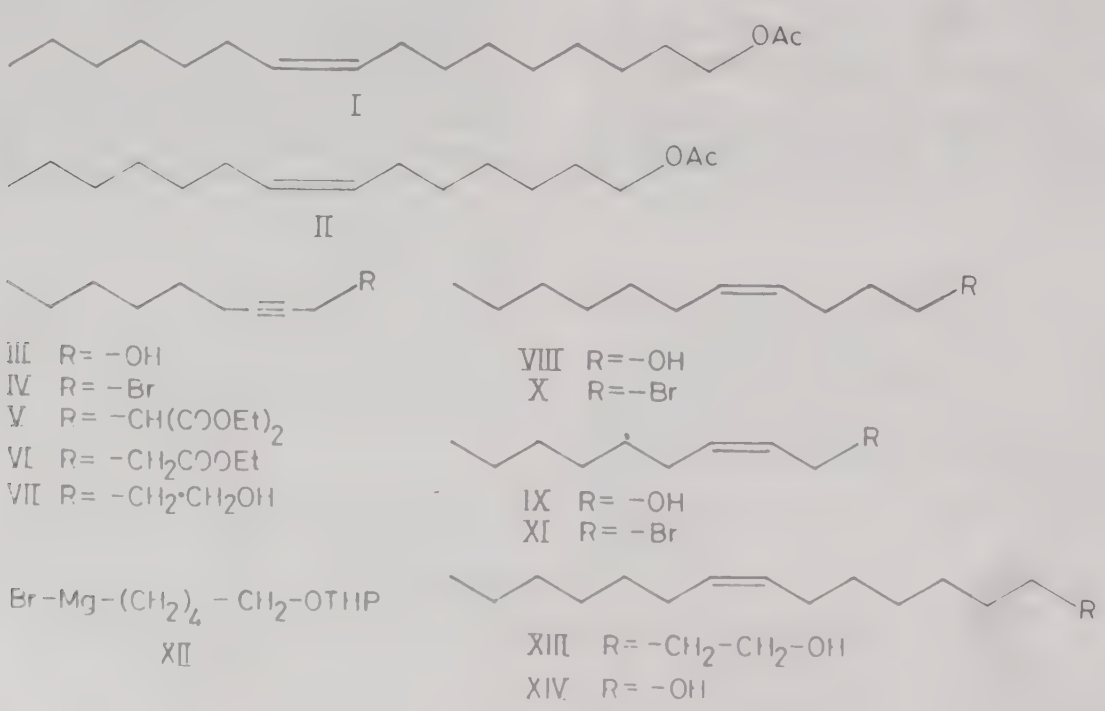
Non-2-yn-1-ol(III) on treatment with PBr_3, pyridine furnishes the bromide(IV) which reacts with ethylmonosodiomalonate to yield the diester(V). Decarbethoxylation of V followed by LAH reduction of the resultant ester(VI) gives the alcohol(VII) which on hydrogenation over Lindlar's catalyst furnishes undec-4Z-en-1-ol(VIII). The alcohol(III) when hydrogenated catalytically provides non-2(*Z*)-en-1-ol(IX). Reactions of VIII and IX with PBr_3/pyridine yield the corresponding bromides (X) and (XI) which on coupling with the Grignard reagent(XII), prepared from 5-bromo-1-tetrahydropyranyloxypentane, in the presence of Li_2CuCl_4, followed by hydrolysis, furnish the alcohols(XIII) and (XIV), respectively. Acetylation of XIII and XIV provides the title acetates (I) and (II), respectively.

One of the active sex pheromone components of rice green caterpillar, *Noranga aenescens*, the most harmful pest insect of the rice plant in eastern Asia, was isolated by Ando and coworkers[1,2] and characterised as (*Z*)-9-hexadecen-1-yl acetate[1,2](I). It is also found to be one of the sex pheromone components of the bertha armyworm, *Mamestra configurata*[3].

Another sex pheromone isolated from the female *Amathes C. nigrum*, found both in Japan[4] and Germany[5], was characterised as (*Z*)-7-tetradecen-1-yl acetate(II). Out of the two forms only the larger flying form of this species showed great activity for (*Z*)-7-tetradecen-1-yl acetate[4]. Literature reports the syntheses of I[4,6,7] and II[4]. Herein we report facile syntheses of these sex pheromones.

I-Bromonon-2-yne(IV), obtained from the alcohol[8](III), by treatment with PBr_3/pyridine, was reacted with ethylmonosodio malonate to afford the diester(V). Decarbethoxylation[9] of V in the presence of moist NaCl/DMSO at 180° followed by LAH reduction of the monoester (VI) afforded the carbinol (VII). The triple bond in VII was catalytically hydrogenated in *n*-hexane in the presence of Lindlar's catalyst[10] and a few drops of quinoline, to get VIII having a *cis* double bond VIII was transformed into the bromide (X) as usual. The bromide (X) was coupled with the Grignard reagent (XII) prepared from 5-bromo-1-tetrahydropyranyloxypentane in the presence of Li_2CuCl_4 (ref. 11) under an inert atmosphere at low temperature to obtain XIII after deprotecting the product with methanol/PTS. Acetylation of XIII with acetic anhydride and pyridine led to the pheromone component I, which was purified by column chromatography over neutral alumina. The IR and PMR data and elemental analyses of synthetic I were compatible with its structure and were also in good agreement with those reported in literature.

For the synthesis of II, 1-bromonon-2(*Z*)-ene(XI),



obtained from III[8], was subjected to the same reaction sequence as X.

Experimental Procedure

Boiling points are uncorrected. Unless otherwise stated all organic extracts were dried over anhydrous Na_2SO_4. Purity of all analytical samples was checked by TLC. IR spectra (thin films, ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer model 377 spectrophotometer and 90 MHz PMR spectra (chemical shifts in δ, ppm) were taken in CCl_4 or $CDCl_3$ using TMS as an internal standard on a Varian EM-390 instrument.

1-Bromonon-2-yne (IV)

To a cooled, stirred solution of III[8] (15 g) in dry ether (200 ml) containing a few drops of dry pyridine, was added PBr_3 (5.1 ml) in dry ether (20 ml) during 30 min. The reaction mixture was kept overnight at room temperature, refluxed for 2 hr, cooled and poured into ice-water. It was extracted with ether, organic extract washed with aq. $NaHCO_3$ (5%), water and dried. Solvent removal gave IV (17.4 g, 80%) which was used as such for the next reaction. Its IR spectrum was flat in the OH region.

Ethyl 2-carbethoxy-undec-4-yn-1-oate (V)

Ethylmonosodiomalonate, prepared from diethyl malonate (17.8 g) and molecularised sodium (21.3 g) in dry benzene (400 ml) and DMF (15 ml), was treated with IV (17.4 g) in dry benzene (80 ml). The reaction mixture was kept overnight at room temperature, refluxed on a steam-bath for 20 hr, cooled, decomposed with water, extracted with benzene and the organic extract dried. Solvent removal followed by distillation under reduced pressure afforded V (12.0 g, 5%); b.p. 175-76°/6-7 mm; IR: 2940, 2860, 2330, 2250, 1720-30 and 1040.

Ethyl undec-4-yn-1-oate (VI)

The diester (V, 12 g) was heated at 170-80° with NaCl (1 g), water (1 ml) and DMSO (100 ml) in an oil-bath for 8 hr. DMSO was removed under reduced pressure, the residue cooled, water added and extracted with ether. The ether layer was washed with water and dried. Solvent removal and distillation of the residue under reduced pressure afforded VI (5.3 g, 60%); b.p. 140-42°/6-7 mm; IR: 2940, 2865, 2330, 2250, 1725, 1452, 1375 & 1045.

Undec-4-yn-1-ol (VII)

To a cooled, stirred suspension of LAH (1.0 g) in anhydrous ether was added dropwise a solution of VI (5.3 g) in dry ether (25 ml). The reaction mixture was left overnight, thereafter it was refluxed for 10 hr, cooled, decomposed with saturated aq. sodium potassium tartrate, extracted with ether and the ether extract dried. Solvent removal and distillation of the residue under reduced pressure followed by column chromatographic purification of the residue over neutral alumina furnished VII (2.9 g, 70%); b.p. 148-50°/7 mm; IR: 3400, 2940, 2860, 2330, 2250, 1450, 1360, 1060; PMR: 0.97 (3H, *t*, $-CH_3$), 1.28-1.65 (10H, *m*, saturated methylenes), 2.25 (4H, *m*, allylic protons), 3.78 (2H, *t*, $-CH_2OH$).

Undec-4(Z)-en-1-ol (VIII)

The alkynol (VII, 2 g) was hydrogenated over Lindlar's catalyst in dry *n*-hexane (20 ml) containing 2 drops of quinoline. A slight positive pressure of hydrogen was applied and then stirred mechanically. When one equivalent of hydrogen was taken up, the catalyst was filtered off, the filtrate successively washed with dil acetic acid, water, aq. sodium bicarbonate (5%), water and dried. Solvent removal and chromatographic purification of the residue over silica gel column (pet. ether-ether, 6:1 as eluent afforded VIII (1.8 g, 90%); IR: 3400, 2945, 2865, 1455, 1370, 1055 & 730.

1-Bromoundec-4(Z)-ene(X)

The alcohol (VIII, 1.8 g) in dry ether (80 ml), was treated slowly with PBr_3 (0.5 ml) in the presence of dry pyridine (2 drops) at 0°C. The reaction mixture was left overnight at room temperature, refluxed for 2 hr, cooled, decomposed with water, worked-up as usual and dried. Evaporation of solvent afforded X which was passed through a short silica gel column using pet. ether as eluent to afford pure X (2 g, 82%).

(Z)-9-Hexadecen-1-ol (XIII)

The Grignard reagent [from dry magnesium turnings (0.2 g) and 5-bromo-1-tetrahydropyranyl-oxypentane (2.1 g) in anhydrous THF (25 ml)] under an inert atmosphere was cooled in an ice-bath and the bromide (X, 2.0 g) in dry THF (20 ml) was added to it during 20 min. After stirring the mixture at $-10°$ for 30 min catalytic amount of Li_2CuCl_4 was introduced. The contents were stirred for 6 hr at 0 to $-10°$ and left overnight at room temperature. The reaction mixture was decomposed with a saturated aq NH_4Cl, extracted with ether, the ether extract washed with water and dried. Solvent removal followed by column chromatography of the residue over neutral alumina using ether (2%) in hexane as eluent afforded the coupled product; IR: 2950, 2870, 1460, 1375, 1080, 1040, 915, 875, 820, 730. The product (1.3 g) was refluxed in methanol/PTS for 3 hr, cooled and $NaHCO_3$ added till reaction ceased. The reaction mixture was filtered and methanol from the filtrate removed under diminished pressure. To the residue

was added a little water, extracted with ether, the ethereal extract washed with brine and dried. Solvent removal afforded XIII (0.7 g, 75%); IR: 3390, 2945, 2870, 1065, 725; PMR($CDCl_3$): 0.93 (3H, *t*, $-CH_3$) 1.3 20H, *s*, $(-CH_2-)_{10}$, 1.91-2.19 (4H, *m*, allylic protons), 3.61 (2H, *t*, $-CH_2OH$), 5.38 (2H, *m*, olefinic protons).

(*Z*)-9-*Hexadecen*-1-*yl acetate* (*I*)

The alcohol (XIII, 0.7 g) was stirred with pyridine (1 ml) and acetic anhydride (2 ml) for 24 hr at room temperature. To this a little water was added and extracted with ether. The ether extract was washed successively with cold dil HCl, water, aq. $NaHCO_3$ (5%) and water and dried. Solvent removal and column chromatographic purification of the residue afforded I (0.5 g, 68%); IR: 2940, 2865, 1740, 1450, 1370, 1235, 1040, 730; PMR($CDCl_3$): 0.92 (3H, *t*, $-CH_3$), 1.32 [20H, *s*, $(-CH_2-)_{10}$], 2.0 (7H, *m*, allylic protons, $-COCH_3$), 4.07 (2H, *t*, $-CH_2-OCOCH_3$), 5.40 (2H, *m*, $-CH=CH-$) (Found: C, 76.6; H, 12.15. Calc. for $C_{18}H_{34}O_2$: C, 76.5; H, 12.1%).

(*Z*)-7-*Tetradecen*-1-*ol* (*XIV*)

The Grignard reagent was prepared by the addition of 5-bromo-1-tetrahydropyranyloxypentane (2.5 g) dissolved in THF (20 ml) to a suspension of dry magnesium turnings (0.23 g) in dry THF (2 ml) under N_2 atmosphere at room temperature. After completion of reaction, the reagent was cooled to $-5°$ and 1-bromonon-2(*Z*)-ene (XI, 2.0 g) in dry THF (20 ml) added to it. After stirring for 30 min, catalytic amount of Li_2CuCl_4 was injected into the reaction mixture and the contents were stirred at $-5°$ for 5 hr and worked-up as usual. Solvent was removed, the residue purified chromatographically over silica gel column using hexane-ether (24:1) as eluent to get the coupled product (1.4 g, 50%); IR: 2930, 2870, 1040, 915, 875, 820, 720; PMR: 0.92 (3H, *t*, $-CH_3$), 1.2-1.82 (22H, *m*, saturated methylenes), 2.09 (4H, *m*, allylic protons), 3.23-3.95 (4H, *m*, $-CH_2-O-CH-O-CH_2-$), 4.54 (1H, *s*, $-O-CH-O-$), 5.48-5.68 (2H, *m*, $-CH=CH-$). This product (1.4 g) was refluxed with methanol/PTS for 4 hr and worked-up as usual. Solvent removal followed by column chromatographic purification over neutral alumina gave XIV (0.8 g, 83%); IR: 3430, 2935, 2870, 1045, 720; PMR: ($CDCl_3$): 0.9 (3H, *t*, $-CH_3$), 1.3 (16H, *s*, saturated methylenes), 2.04 (4H, *m*, allylic protons), 3.58 (2H, *t*, $-CH_2OH$), 5.47-5.65 (2H, *m*, $-CH=CH-$).

(*Z*)-7-*Tetradecen*-1-*yl-acetate*(*II*)

The alcohol (XIV, 0.8 g) was stirred with dry pyridine (1 ml) and acetic anhydride (2 ml) for 24 hr under anhydrous conditions at room temperature. Usual work-up, as mentioned for I, followed by solvent removal and purification of the crude product over neutral alumina afforded II (0.5 g, 60%); IR: 2950, 2880, 1740, 1238, 1030, 720; PMR: 0.95 (3H, *t*, $-CH_3$), 1.35 (16H, *s*, saturated methylenes), 2.0 (3H, *s*, $-CO-CH_3$), 2.15 (4H, *m*, allylic methylenes), 3.93 (2H, *t*, $-CH_2-CH_2-O-CO-$), 5.42-5.65 (2H, *m*, $-CH=CH-$) (Found: C, 75.6; H, 11.9. Calc. for $C_{16}H_{30}O_2$: C, 75.5; H, 11.9%).

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Solid Phase Synthesis of Substance P & Its Analogues Employing 9-Fluorenylmethoxycarbonylamino Acid Active Esters

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Substance P and six of its analogues containing D-*p*-hydroxyphenylglycine at positions 7 and/or 8 have been synthesized employing fluorenylmethoxycarbonylamino acid (Fmoc) active esters and *p*-alkoxybenzyl alcohol resin. Diethylamine is employed for the cleavage of Fmoc-group. The agonistic and antagonistic activities of the peptides have been studied.

The introduction of the base-labile 9-fluorenylmethoxycarbonyl (Fmoc) group for amino protection[1] has added a new dimension to solid phase peptide synthesis. Prior to Fmoc acid-labile N-protecting groups were usually employed for amino acids during peptide synthesis and this necessitated repeated acidolysis which had many undesirable side effects[2]. The Fmoc group, being cleaved by mild non-hydrolytic bases, obviates the need for acidolysis; further, it permits the use of an acid-sensitive solid phase like *p*-alkoxybenzyl alcohol resin[3]. This combination of Fmoc-amino acids and *p*-alkoxybenzyl alcohol resin has been successfully employed in the synthesis of somatostatin[4], wherein Fmoc-amino acid symmetrical anhydrides in large excess (six-fold) were generally employed. However, use of Fmoc-amino acid active esters in the presence of 1-hydroxybenzo triazole (HOBt) permits the synthesis of peptides with lesser quantities of the expensive Fmoc-derivatives as demonstrated by the synthesis of [Leu – NH_2][5]-enkephalin[5] and Oxytocin[6] and this procedure has now been extended for the solid phase synthesis of substance P (SP) and its analogues. For Fmoc-cleavage the milder base diethylamine is employed instead of the commonly employed piperidine; but the duration of deprotection extends to about 2 hr. This confirms our earlier observation on the use of diethylamine for Fmoc-Cleavage in the solid phase synthesis of enkephalin analogues[8]. The Fmoc group was employed for N^{α}-protection of all amino acids except arginine for which the benzyloxycarbonyl (Z) group was used. If Fmoc group had been employed for the protection of α-NH_2 function of arginine it would have been cleaved partially during the ammonolysis step necessary for the cleavage of the peptide from the resin. Further, the basic side chain functionalities of lysine and arginine are protected by Z and nitro groups, respectivley. The synthesis of SP is schematically represented in Chart 1.

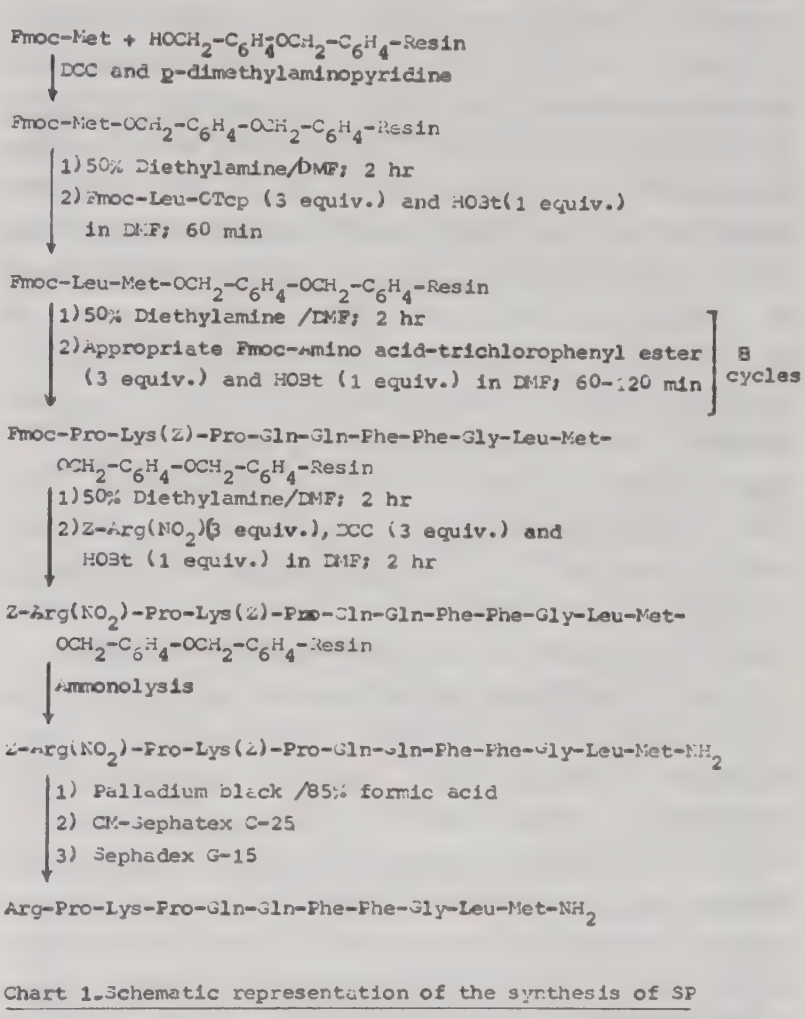
Fmoc-Met + HOCH2-C6H4-OCH2-C6H4-Resin
DCC and p-dimethylaminopyridine
Fmoc-Met-OCH2-C6H4-OCH2-C6H4-Resin
1) 50% Diethylamine/DMF; 2 hr
2) Fmoc-Leu-OTcp (3 equiv.) and HOBt(1 equiv.) in DMF; 60 min
Fmoc-Leu-Met-OCH2-C6H4-OCH2-C6H4-Resin
1) 50% Diethylamine /DMF; 2 hr
2) Appropriate Fmoc-amino acid-trichlorophenyl ester (3 equiv.) and HOBt (1 equiv.) in DMF; 60-120 min
8 cycles
Fmoc-Pro-Lys(Z)-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-
OCH2-C6H4-OCH2-C6H4-Resin
1) 50% Diethylamine/DMF; 2 hr
2) Z-Arg(NO2)(3 equiv.), DCC (3 equiv.) and HOBt (1 equiv.) in DMF; 2 hr
Z-Arg(NO2)-Pro-Lys(Z)-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-
OCH2-C6H4-OCH2-C6H4-Resin
Ammonolysis
Z-Arg(NO2)-Pro-Lys(Z)-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH2
1) Palladium black /85% formic acid
2) CM-Sephatex C-25
3) Sephadex G-15
Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH2

Chart 1. Schematic representation of the synthesis of SP

The first amino acid methionine was anchored to *p*-alkoxybenzyl alcohol resin by reacting Fmoc-Met with the resin using dicyclohexylcarbodiimide (DCC) in the presence of *p*-dimethylaminopyridine according to the procedure of Meienhofer *et al*[9]. The methionine content of the resin in the resulting Fmoc-Met-$OCH_2-C_6H_4-OCH_2-C_6H_4$-resin was estimated spectrophotometrically and found to be 0.31 mmol/g of the resin. The Fmoc-amino acyl resin was deprotected by

treatment with 50% diethylamine in dimethylformamide (DMF) for 2 hr followed by the addition of Fmoc-Leu-OTcp (3 equiv) in the presence of HOBt (1 equiv). The coupling was found to be complete in about 1 hr as revealed by Kanser's ninhydrin test[10], resulting in Fmoc-Leu-Met-$OCH_2-C_6H_4-OCH_2-C_6H_4$-resin. This cycle of deprotection with 50% diethylamine/DMF and coupling with 3 equivalents of Fmoc-amino acid trichlorophenyl ester in the presence of 1 equivalent of HOBt was repeated to introduce the following eight amino acid residues: Gly, Phe_2, Gln_2, Pro, Lys, and Pro. In each cycle, a reaction time of 2 hr was allowed for deprotection. Each coupling reaction took about 1 to 2 hr for completion. The coupling of arginine by active ester/HOBt method did not proceed to completion even after repeated additions of the amino acid derivative. Therefore, it was decided to add this amino acid by the DCC/HOBt method. Thus, Z-Arg(NO_2) (3 equiv) was added in the presence of DCC (3 equiv) and HOBt (1 equiv). The coupling was complete in about 2 hr yielding the protected SP-resin, Z-Arg(NO_2)-Pro-Lys(Z)-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-$OCH_2-C_6H_4-OCH_2-C_6H_4$-resin. The protected peptide was then severed from the resin with the simultaneous formation of the C-terminal amide bond by subjecting the protected peptide resin to ammonolysis. The product, Z-Arg(NO_2)-Pro-Lys(Z)-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2 was recovered from the solution and purified; yield 67% based on the methionine content of the esterified resin. The protected peptide was subjected to catalytic transfer hydrogenation using palladium black catalyst and 85% formic acid[11,12] to remove all the three protecting groups in a single step in about 2 hr.

In the SP molecule, the amino acids at positions 7 to 11 are essential for activity[13]. Substitutions in these positions, especially Phe[7], leads to analogues with considerably reduced activity. The replacement of these amino acids by D-amino acids leads to analogues that are almost inactive as agonists but such analogues possess antagonistic properties[14]. The SP antagonists so far known are generally found to contain D-amino acids in positions 7 to 9. In view of these findings, it was decided to synthesise a few analogues of SP containing D-amino acid residues in positions 7 and 8, and to study their agonistic and antagonistic activities. Consequently, three SP analogues, in which positions 7 and/or 8 were substituted by the unnatural amino acid D-*p*-hydroxyphenylglycine [D-Gly(*p*-OH-phenyl)], were synthesized. The analogues synthesized were [D-Gly(*p*-OH-phenyl)]^7-SP. The three intermediate octapeptide fragments, [D-Gly(*p*-OH-phenyl)]^7-SP(4-11), [D-Gly(*p*-OH-phenyl)]^8-SP(4-11) and [D-Gly(*p*-OH-phenyl)]^{7,8}-SP(4-11) were also isolated and biologically assayed.

The methods and materials employed for the synthesis of these analogues were essentially the same as those employed for the synthesis of SP described above.

The salient features of the synthesis are: (i) A single addition of 3 equivalents of Fmoc-amino acid trichlorophenyl ester and 1 equivalent of HOBt in DMF for each coupling was sufficient to complete the reaction, the duration being 1-2 hr. Only in the case of Z-Arg(NO_2), the DCC/HOBt method had to be employed; (ii) excess of amino acid active esters could be recovered and reused; (iii) yield of the final product was good and the product needed minimum purification; and (iv) peptide anchored to *p*-alkoxybenzyl alcohol resin could be conveniently released from the solid support with the simultaneous formation of the C-terminal amide bond in a single ammonolysis step.

Biological activities

The biological assays were performed at the Government College of Pharmacy, Bangalore. Four different assay systems were employed for estimating the activities of SP and its analogues.

(*i*) *Contraction of the isolated guinea pig ileum*[15]

The agonistic and antagonistic activities of SP and its analogues were tested by the contraction of the isolated guinea pig ileum. In contracting isolated strips of guinea pig ileum, SP prepared by us was as active as an authentic sample of SP. The analogues of SP showed weak contractions only at a high dose of 200 μg, whereas SP acted at nanogram dosage. Further, the analogues, did not antagonize the contractions induced by 100-500 ng doses of SP even at a high dose of 200 μg.

(*ii*) *Analgesic activity* (*Hot plate method*)[16]

On intravenous injections at doses of 2.5 mg/kg to 5 mg/kg, SP showed analgesia which lasted for about 1 hr. The analogues did not show any analgesia upto a dose of 10 mg/kg.

(*iii*) *Effect on blood vessels* (*Rat hind limb preparation*)[17]

In the rat, the infusion of SP into the abdominal artery increased the blood flow in a dose dependent way from 5 μg to 30 μg, but the rate of flow remained constant above 30 μg dose. The analogues showed increase in the blood flow only at a high dose of 200 μg, the blood flow being equivalent to that caused by 10 μg of SP.

(*iv*) *Effect on dog blood pressure*[17]

Intravenous injections of SP in doses from 20 to 80 ng/kg into the femoral vein of the dog caused a fall in

blood pressure which was not dose-dependent. However, the recovery time increased with dose. The analogues caused a fall in blood pressure at a dose of 20 μg/kg, the fall in pressure and the recovery time being equivalent to those caused by 20-80 ng/kg doses of SP.

From the biological activities exhibited by SP and its analogues it may be concluded that replacemment of Phe[7] or Phe[8] by D-Gly(*p*-OH-phenyl) results in negligible or weak agonistic activity. Similar observations have been made by other investigators when other D-amino acids are substituted in these positions. However, contrary to our expectations, the analogues did not exhibit any antagonistic activities even at high doses. This is presumably due to the inability of these analogues to compete effectively with SP for SP-receptors.

Experimental Procedure

All the amino acids employed except glycine were of L-configuration unless otherwise specified. Melting points were determined using Leitz-Wetzlar melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on silica gel G plates using the following solvent systems: (A) chloroform – methanol – acetic acid (40:2:1); (B) chloroform – methanol – water (8:3:1, lower phase); (C) *n*-butanol – pyridine – acetic acid – water (30:20:6:24); and (D) *n*-butanol – acetic acid – water (4:1:5, upper phase). The R_f values are designated as R_fA, R_fB, R_fC and R_fD respectively. For amino acid analyses samples were hydrolyzed with 6*N* HCl at 110° for 24 hr.

Fmoc-amino acids were prepared by the method of Change *et al.*[18] and Fmoc-amino acid trichlorophenyl esters according to the method of Sivanandaiah and Gurusiddappa[19]. The following amino acid derivatives which have not been reported earlier were also employed during the present investigations.

Fmoc-Lys(Z)

N^{ε}-Z-Lys was reacted with 9-fluorenylmethyl chloroformate according to the reported procedure[18] to yield Fmoc-Lys(Z) as an oil in 74% yield; R_fA, 0.58.

Fmoc-Lys(Z)-OTcp

The reaction of Fmoc-Lys(Z) with trichlorophenol in the presence of DCC according to the reported procedure[19] resulted in Fmoc-Lys(Z)-OTcp in 65% yield; R_fA 0.71; m.p., 112-14°; $[\alpha]_D^{25} -16°$ (*c*, 1; DMF) (Found: C, 61.5; H, 4.4; N, 4.2. $C_{35}H_{31}O_6N_2Cl_3$ requires C, 61.7; H, 4.6; N, 4.1%).

Fmoc-Pro-OTcp

The reaction of Fmoc-Pro with trichlorophenol in the presence of DCC as above afforded Fmoc-Pro-OTcp in 76% yield; R_fA, 0.66; m.p., 122-24°; $[\alpha]_D^{25} -52°$ (*c*, 1; DMF) (Found: C, 60.24; H, 3.8; N, 2.8. $C_{26}H_{20}O_4NCl_3$ requires C, 60.5; H, 3.9; N, 2.7%).

Synthesis of SP

Fmoc-Met-$OCH_2-C_6H_4-OCH_2-C_6H_4$-resin

Fmoc-Met (3.71 g, 10 mmol) was reacted with *p*-alkoxybenzyl alcohol resin (6 g) using DCC (2.06 g, 10 mmol) and *p*-dimethylaminopyridine (1.22 g, 10 mmol) in CH_2Cl_2 – DMF (4:1, 120 ml) for 20 hr according to the procedure of Meienhofer *et al.*[9] to afford the title Fmoc-amino acyl resin; yield, 6.81 g; methionine content, 0.31 mmol/g of the resin.

Fmoc-Gly-Leu-Met-$OCH_2 \div C_6H_4-OCH_2-C_6H_4$-resin

The above Fmoc-aminoacyl resin (6.71 g, 2.06 mmol) was taken in a horizontal solid phase vessel and peptide synthesis was carried out manually. All washings and reactions were carried out using 10 ml portions of solvents per gram of resin. Completion of coupling in each cycle was assessed by Kaiser's test. Each cycle of the synthesis consisted of the following operations:

1. Washing with CH_2Cl_2	2 × 2 min
2. Washing with DMF	2 × 2 min
3. Deblocking with 50% diethylamineDMF	1 × 120 min
4. Washing with DMF	2 × 2 min
5. Washing with water-dioxane (1:2)	2 × 5 min
6. Washing with DMF	2 × 2 min
7. Washing with CH_2Cl_2	3 × 2 min
8. Washing with DMF	3 × 2 min

9. Coupling with 3 equiv of Fmoc-amino acid-trichlorophenyl ester in DMF in the presence of 1 equiv of HOBt.

10. Washing with DMF	3 × sucessively,
11. Washing with isopropanol	
12. Washing with CH_2Cl_2	2 min each.

The time taken for the coupling of each amino acid is given in Table 1. After completion of the sequence, the protected peptide resin was dried over P_2O_5 *in vacuo*, yield, 7.13 g.

Z-Arg(NO_2)-Pro-Lys(Z)-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-$OCH_2-C_6H_4-OCH_2-C_6H_4$-resin

Fmoc-Gly-Leu-Met-$OCH_2-C_6H_4-OCH_2-C_6H_4$-resin (2.33 g, 0.68 mmol) was subjected to the cycle of operations described above to incorporate the remaining amino acid residues. Z-Arg(NO_2) (3 equiv) was coupled in the presence of DCC (3 equiv) and HOBt (1 equiv). The protected SP-resin was dried over P_2O_5 *in vacuo*; yield, 2.81 g.

Table 1 – Duration of Coupling for Each Amino Acid Derivative

Amino acid derivative	Duration of coupling (min)
Fmoc-Leu-OTcp	60
Fmoc-Gly-OTcp	60
Fmoc-Phe-OTcp	60
Fmoc-Gln-OTcp	75
Fmoc-Pro-OTcp	75
Fmoc-Lys(Z)-OTcp	90
Fmoc-D-Gly(*p*-OH-phenyl)-OTcp	120
Z-Arg(NO_2)(DCC/HOBt)	120

Z-Arg(NO_2)-Pro-Lys(Z)-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2

The protected SP-resin (2.8 g) was suspended in absolute methanol (150 ml) and allowed to stand for 2 hr. The suspension was stirred at $-10°$ and saturated with dry ammonia (distilled over sodium). Stirring was continued at $-10°$ for 3 hr and for 72 hr at 0°. The resin was filtered off and washed with warm methanol and DMF. The combined filtrate was evaporated to dryness. The residue was again evaporated with additional amounts of methanol to expel ammonia completely, dissolved in minimum amount of methanol and precipitated by adding ether. The solid was isolated and precipitated again using DMF-ethyl acetate. Yield, 0.76 g (67.3%). A sample for analysis was further purified by column chromatography over silica gel using the solvent system *n*-butanol-acetic acid (HOAc)-water (4:1:1), m.p., 220-23°; R_fB, 0.55; $[\alpha]_D^{25}$ $-36°$ (*c*, 0.5; DMF) [Reported, m.p. 224-25°; $[\alpha]_D^{25}$ $-37°$ (DMF)]. (Found: C, 57.7; H, 6.5; N, 16.2. Calc for $C_{79}H_{109}O_{19}N_{19}S$: C, 57.1; H, 6.6; N, 16.0%).

Amino acid composition

Arg(1)	Pro(2)	Lys(1)	Gln(2)	Phe(2)	Gly(1)	Leu(1)	Met(1)
0.98	1.97	1.03	2.07	1.94	0.99	1.02	0.89

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2.3HOAc

The protected SP (0.33 g, 0.2 mmol) was subjected to catalytic transfer hydrogenation[11,12] using 85% formic acid (1.5 ml, containing 0.2 ml anisole) and freshly prepared palladium black catalyst (0.16 g) for 2 hr. The catalyst was filtered off and the filtrate concentrated to afford crude SP which was purified by ion exchange chromatography over CM-Sephadex C-25 (Pharmacia) using a stepwise gradient of ammonia acetate buffer (*p*H 5). SP was then subjected to gel filtration over Sephadex G-15 using 0.5 *M* acetic acid, yield, 0.2 g (65.4%; overall yield was 44% based on the methionine content of the original esterified resin); R_fC, 0.53; $[\alpha]_D^{25}$ $-80°$ (*c*, 0.5; 5% HOAc) [Reported[20], $[\alpha]_D^{27}$ $-76°$ (*c*, 0.4; 5% HOAc)].

Synthesis of SP Analogues

Pro-Gln-Gln-D-Gly(p-OH-phenyl)-Phe-Gly-Leu-Met-$OCH_2-C_6H_4-OCH_2-C_6H_4$-Resin (I), Pro-Gln-Gln-Phe-D-Gly(p-OH-phenyl)-Gly-Leu-Met-$OCH_2-C_6H_4-OCH_2-C_6H_4$-Resin (II) and Pro-Gln-D-Gly(p-OH-phenyl)-D-Gly(p-OH-phenyl)-Gly-Leu-Met-$OCH_2-C_6H_4-OCH_2-C_6H_4$-resin (III)

Fmoc-Gly-Leu-Met-$OCH_2-C_6H_4-OCH_2-C_6H_4$-resin (4.78 g, 1.38 mmol) was divided into three equal parts (1.59 g each, 0.46 mmol) and the synthesis was continued with each part of the resin separately following the same sequence of operations described above but incorporating the appropriate amino acid residues to get the title peptide resins I to III.

Z-Arg(NO_2)-Pro-Lys(Z)-Pro-Gln-Gln-D-Gly(p-OH-phenyl)-Phe-Gly-Leu-Met-$OCH_2-C_6H_4-OCH_2-C_6H_4$-Resin (IV), Z-Arg($NO_2$)-Pro-Lys(Z)-Pro-Gln-Gln-Phe-D-Gly(p-OH-phenyl)-Gly-Leu-Met-$OCH_2-C_6H_4-OCH_2-C_6H_4$-resin (V), and Z-Arg($NO_2$)-Pro-Lys(Z)-Pro-Gln-Gln-D-Gly(p-OH-phenyl)-D-Gly(p-OH-phenyl)-Gly-Leu-Met-$OCH_2-C_6H_4-OCH_2-C_6H_4$-Resin (VI)

Each of the peptide resins (I to III) was divided into two equal parts and synthesis was continued as before with one part of each resin. The last amino acid derivative Z-Arg(NO_2) (3 equiv) was added in the presence of DCC (3 equiv) and HOBt (1 equiv) as for SP. After completion of the sequence, each protected peptide resin (IV to VI) was washed and dried as described earlier.

The duration of coupling for each amino acid residue is given in Table 1.

Pro-Gln-Gln-D-Gly(p-OH-phenyl)-Phe-Gly-Leu-Met-NH_2.HOAc (VII), Pro-Gln-Gln-Phe-D-Gly(p-OH-phenyl)-Gly-Leu-Met-NH_2.HOAc (VIII), and Pro-Gln-Gln-Gly(p-OH-phenyl)-D-Gly(p-OH-phenyl)-Gly-Leu-Met-NH_2.HOAc (IX)

Each peptide resin (I to III) was suspended in absolute methanol (75 ml/g of resin) and subjected to ammonolysis as described for the protected SP-resin. The peptides after precipitation from methanol – ether and DMF-ethyl acetate were subjected to gel filteration over Sephadex G-15 (1.5 cm × 120 cm) using 0.5 *M* acetic acid for elution. The yields and physical constants of the peptides (VII-IX) are given in Table 2.

Z-Arg(NO_2)-Pro-Lys(Z)-Pro-Gln-Gln-D-Gly(p-OH-phenyl)-Phe-Gly-Leu-Met-NH_2(X), Z-Arg(NO_2)-Pro-Lys(Z)-Pro-Gln-Gln-Phe-D-Gly(p-OH-phenyl)-Gly-Leu-Met-NH_2 (XI) and Z-Arg(NO_2)-Pro-Lys(Z)-Pro-Gln-Gln-D-Gly (p-OH-phenyl)-D-Gly (p-OH-phenyl)-Gly-Leu-Met-NH_2(XII.

Table 2 – Physical Properties and Elemental Analyses of Peptides (VII to XII)

Peptide	Yield (%)	m.p. (°C)	R_f	$[\alpha]_D^{25}$*	Mol. formula	Calc (found) %		
						C	H	N
Pro-Gln-Gln-D-Gly(*p*-OH-phenyl)-Phe-Gly-Leu-Met-NH_2(VII)	63	178-83	0.38 (D)	−68°	$C_{47}H_{69}N_{11}O_{13}S$	54.91 (55.28	6.77 6.92	14.99 14.76)
Pro-Gln-Gln-Phe-D-Gly(*p*-OH-phenyl)-Gly-Leu-Met-NH_2(VIII)	64.5	180-85	0.39 (D)	−64°	$C_{47}H_{69}N_{11}O_{13}S$	54.91 (54.66	6.77 7.01	14.99 14.88)
Pro-Gln-Gln-D-Gly(*p*-OH-phenyl)-D-Gly(*p*-OH-phenyl)-Gly-Leu-Met-NH_2(IX)	62	176-81	0.31 (D)	−52°	$C_{46}H_{67}N_{11}O_{14}S$	53.64 (54.02	6.56 6.73	14.96 15.31)
Z-Arg(NO_2)-Pro-Lys(Z)-Pro-Gln-Gln-D-Gly(*p*-OH-phenyl)-Phe-Gly-Leu-Met-NH_2(X)	64	162-65	0.43 (B)	−34°	$C_{78}H_{107}N_{19}O_{20}S$	56.35 (56.11	6.44 6.53	16.01 16.28)
Z-Arg(NO_2)-Pro-Lys(Z)-Pro-Gln-Gln-Phe-D-Gly(*p*-OH-phenyl)-Gly-Leu-Met-NH_2(XI)	64.5	158-61	0.42 (B)	−38°	$C_{78}H_{107}N_{19}O_{20}S$	56.35 (56.02	6.44 6.76	16.01 16.23)
Z-Arg(NO_2)Pro-Lys(Z)-Pro-Gln-Gln-D-Gly(*p*-OH-pheny)-D-Gly(*p*-OH-phenyl)-Gly-Leu-Met-NH_2(XII)	61	174-77	0.39 (B)	−46°	$C_{77}H_{105}N_{19}O_{21}S$	55.56 (56.20	6.31 6.64	15.99 15.09)

* For VII-IX, *c*, 0.5; 5% HOAc; and for X-XII, *c*, 0.5; DMF

Table 3 – Amino Acid Composition of Peptides X to XII

Peptide	Amino acid composition								
	Arg	Pro	Lys	Gln	Phe	D-Gly-(*p*-OH-phenyl)	Gly	Leu	Met
X	0.98	1.97	1.08	1.98	0.98	0.94	1.00	0.99	0.92
XI	0.97	2.01	0.99	2.10	0.96	0.97	1.02	0.96	0.91
XII	1.01	1.94	1.10	2.04	—	1.92	1.00	0.97	0.94

Each protected peptide resin (IV to VI) was subjected to ammonolysis as described earlier. The peptides were precipitated from methanol-ether and DMF-ethyl acetate. The yields and physical constants of the peptides (X-XII) are given in Table 2. Samples for analysis were purified by column chromatography on silica gel as described for protected SP. The results of amino acid analysis are given in Table 3.

Arg-Pro-Lys-Pro-Gln-Gln-D-Gly(p-OH-phenyl)-Phe-Gly-Leu-Met-NH_2.3HOAc (XIII), Arg-Pro-Lys-Pro-Gln-Gln-Phe-D-Gly(p-OH-phenyl)-Gly-Leu-Met-NH_2.3HOAc (XIV), and Arg-Pro-Lys-Pro-Gln-Gln-D-Gly(p-OH-phenyl)-D-Gly(p-OH-phenyl)-Gly-Leu-Met-NH_2.3HOAc (XV).

Each protected SP analogue (X to XII) was subjected to catalytic transfer hydrogenation using 85% formic acid and palladium black. The free peptides were isolated and purified by ion exchange chromatography and gel filtration as described for SP. The yields of the peptides (XIII-XV) based on the *original resin esterification level are*: *XIII*, 37.7%; XIV, 40%; and XV, 36.9%.

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Notes

Oxidative Rearrangement of 5 α-Cholestane-3-one with Thallic Nitrate

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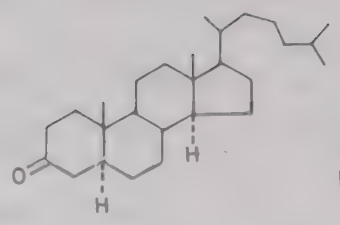
5 α-Cholestane-3-one (**1**) on treatment with thallic nitrate in acetic acid at room temperature undergoes single-step, facile oxidative rearrangement with ring-contraction to yield a mixture of epimers 2α- and 2β-carboxy-A-nor-5α-cholestanes (**3** and **4**) in which **3** predominates. Pure **3** can be obtained by resolution with dehydroabietyl amine. Structure of **3** has been decided on the basis of its spectral data which are similar to those reported in the literature.

In recent years the use of thallic nitrate as a reagent for oxidative rearrangement of organic compounds has been reported by several workers[1-9]. This reagent has also been used to some extent in the case of steroids[10,11]. The reaction conditions are simple and the yields usually high.

As an example from steroids, we have not found that 5α-cholestane-3-one (**1**), when treated with thallic nitrate at room temperature undergoes single step, facile oxidation with ring-contraction to form a pair of epimers characterised as 2α- and 2β-carboxy-A-nor-5α-cholestanes (**3** and **4**) in which **3** predominates. The compound **3** has been previously obtained as Favorskii rearrangement product of 2α-bromo-cholestane-3-one[12] and by the photochemical Wolff rearrangement of 2-diazo-5α-cholestane-3-one[13]. However, the present method is simple and may be useful for preparing products obtainable by rearrangements of other rings in steroids leading to newer kinds of compounds.

The products formed from **1** could be a pair of epimers **3** and **4** or **8** and **9** with the carboxy attachment either in position 2 or 3 or in both, in ring-A. However, on mechanistic and stereochemical ground position-2 is preferred. The first step in the process is enolisation. The formation of $\Delta^{2,3}$-enol (**2**) seems to be more plausible over the $\Delta^{3,4}$-enol (**7**), in view of the *trans*-geometry of the A/B ring junction in **1**. The predominant acid (**3**) was isolated in the pure state by resolution with dehydroabietyl amine. The pure acid (**3**) and its methyl ester had properties identical with those described in the literature. The mechanism of this



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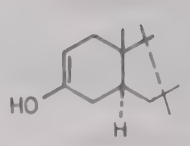

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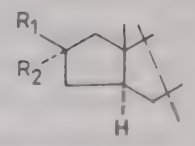
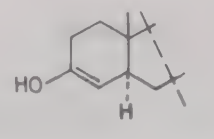


3, R_1 = H; R_2 = COOH
4, R_1 = COOH; R_2 = H
5, R_1 = H; R_2 = COOMe
6, R_1 = COOMe; R_2 = H



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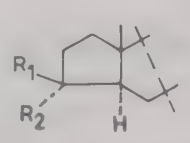

8, R_1 = H; R_2 = COOH
9, R_1 = COOH; R_2 = H

reaction has been discussed by earlier workers. Cava and coworkers have shown that the α-carbomethoxy compound (**5**) can be differentiated from its epimer (**6**) by solvent-dependent NMR studies[12,13].

Conversion of 5α-cholestane-3-one (**1**) *to 2-carboxy-A-nor-5α-cholestanes* (**3** *and* **4**)

To 5α-cholestane-3-one (**1**) (prepared from cholesterol) (300 mg) in acetic acid (12 ml) was added thallic nitrate (900 mg) and the mixture stirred at 27° for 3 hr. Thallium mononitrate, which precipitated out, was filtered off, water (10 ml) added to the filtrate and the mixture extracted with ether and processed as usual. Evaporation of the solvent and crystallisation of the residue from methanol gave the product mixture (**3** and **4**, 280 mg), m.p. 132°-60°; IR (cm^{-1}): 3200, 2700, 1708, 1296, 1246, 1175, 912 (Found: C, 80.3: H, 11.3. Calc. for $C_{27}H_{26}O_2$: C, 80.5; H, 11.5%).

Resolution of the product mixture with dehydroabietyl amine: Isolation of 2α-carboxy-A-nor-5α-cholestane (**3**)

To a solution of dehydroabietyl amine (50 mg) dissolved in methanol (5 ml) was added the above acid-mixture (120 mg). The solution was stirred at 15° for 3 hr, diluted with water (3 ml), the precipitated salt filtered, dried and crystallised from methanol, m.p. 164-67°. Recrystallisation from the same solvent yielded the pure salt (80 mg), m.p. 170-71°.

To the salt (100 mg), dissolved in ether (10 ml) was added a saturated solution of Na_2CO_3 (4 ml). The mixture was shaken thoroughly till all the solid had dissolved. The ether layer was separated and the aqueous layer acidified with conc HCl. The

†The material forms parts of the Ph.D. thesis of P Balakrishnan submitted to the IIT, Bombay in 1977.

precipitated acid after usual work-up and crystallisation from methanol gave **3**, m.p. 172-73° (lit.[12,13] 173-75°); IR: 2960, 1696, 1276, 1252 cm^{-1}, PMR: τ 9.34 (3H, *s*, C_{18}-angular CH_3 group), 9.29 (3H, *s*, C-angular CH_3 group), 9.13 and 9.09 (*d* each, 9H, C_{20}-Me and C_{25}-Me_2) and 7.1 (1H, *m*, C*H*-COOH) (Found: C, 80.6; H, 11.7. Calc. for $C_{27}H_{46}O_2$: C, 80.5; H, 11.5%). The acid **3** on esterification (diazomethane) gave the methyl ester 2α-carbomethoxy-A-nor-5α-cholestane (**5**), crystallised from methanol, m.p. 96-97° (lit.[12,13] 97-98°).

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Synthesis of (6*E*,11*Z*)-6,11-Hexadecadien-1-yl Acetate

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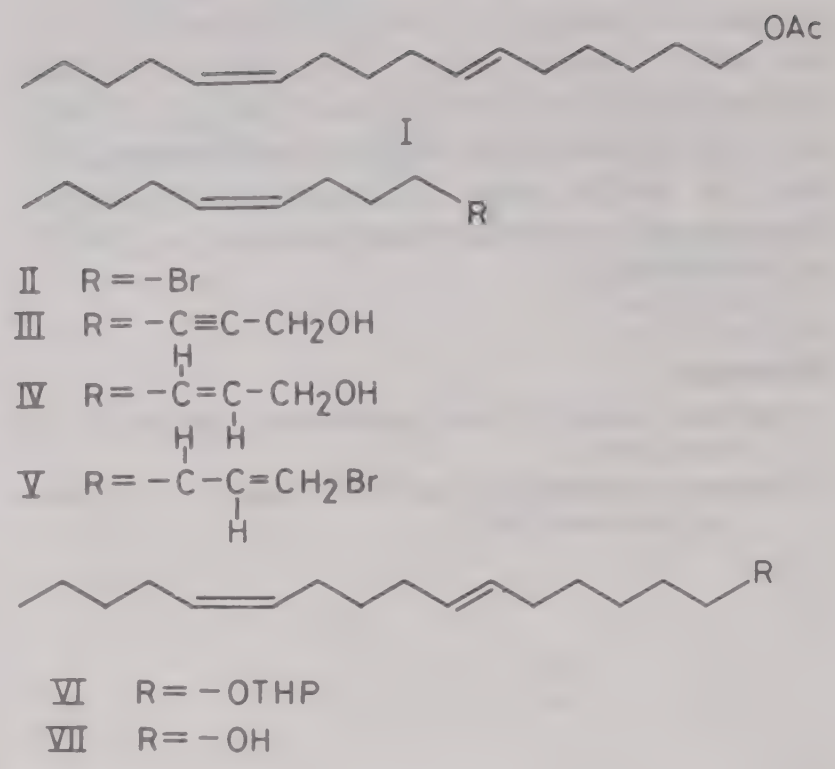
1-Bromo-non-4(*Z*)-ene(II) on reaction with the dianion of propargyl alcohol in liq. NH_3 yields the acetylenic alcohol(III) which on LAH reduction gives (2*E*, 7*Z*)-2,7-dodecadien-1-ol(IV). The bromide (V) obtained from IV when coupled with 1-bromo-4-tetrahydropyranyloxybutane in the presence of Li_2CuCl_4 affords VI which on hydrolysis gives VII. Acetylation of VII (Py/Ac_2O) leads to the title compound(I).



Kochansky *et al.*[1] characterised one of the sex pheromone components of the wild silk moth, *Antheraea polyphemus* (Cramer), as (6*E*, 11*Z*)-6,11-hexadecadien-1-yl acetate(I). Literature reports a number of syntheses of I[2-6]. In continuation of our synthetic work in the field of sex pheromones we report herein a facile synthesis of I.

1-Bromo-non-4(*Z*)-ene(II)[7] was used to alkylate[8] the dilithio derivative of propargyl alcohol in liq. NH_3 to afford the alcohol (III), which on LAH reduction[9] gave the dienol (IV) having the *trans*-stereochemistry at the double bond. Bromination of IV with PBr_3 in the presence of dry pyridine in dry ether led to the corresponding bromide. The bromide(V) was coupled with 1-bromo-4-tetrahydropyranyloxybutane in the presence of a catalytic amount of Li_2CuCl_4 (ref. 10) in THF under N_2 atmosphere to furnish VI. Deprotection of VI with methanol/PTS led to the alcohol(VII) which on acetylation gave the desired I having IR and PMR data identical with those reported in literature.

The boiling points reported are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded as thin films on a Perkin-Elmer 377 and PMR spectra on a EM-390 (90 MHz) instrument using TMS as an internal standard; chemical shifts are expressed in δ-scale. Silica gel G (Acme's) containing plaster of paris (13%) was used for TLC. Unless otherwise mentioned, the organic extracts were dried over anhydrous sodium sulphate.

Dodec-7(Z)-en-2-yn-1-ol (III)

To liquid ammonia (800 ml) containing ferric nitrate (50 mg) was added lithium (0.6 g) in portions with constant stirring. After the disappearance of blue colour, propargyl alcohol (2.7 g) in dry THF (25 ml) was added during 10 min. After stirring for one hr 1-bromo-non-4(*Z*)-ene (II, 10 g) in anhydrous THF (100 ml) was added to the reaction mixture, stirred for another 4 hr and the reaction quenched by adding solid ammonium chloride. Ammonia was allowed to evaporate, the residue washed with brine, extracted with ether and dried. Solvent removal and distillation of the residue under reduced pressure afforded III (4.8 g, 55%); b.p. 160/3-4 mm; IR: 3500-3200, 2290, 2230, 1010 and 720; PMR($CDCl_3$): 0.9 (3H, *t*, $-CH_3$), 1.3 (6H, *m*, saturated methylenes), 2.0-2.33 (6H, *m*, allylic and acetylenic methylenes), 4.12 (2H, *t*, $-CH_2OH$), 5.25-5.45 (2H, *m*, olefinic protons).

(2*E*,7*Z*)-2,7-*Dodecadien*-1-*ol* (IV)

To a well cooled, stirred suspension of LAH (1.5 g) in dry THF (100 ml), was added dropwise III (4.8 g) in dry THF (40 ml). The reaction mixture was left overnight at room temperature and then refluxed for 8 hr. The contents were cooled, decomposed with a saturated solution of sodium potassium tartrate, the ethereal layer decanted and the residue extracted with ether. The combined ether extract was dried, the solvent removed and the residue chromatographed over neutral alumina to procure pure IV (3.8 g, 80%); IR: 3340, 2920, 2860, 1080, 1000, 965 and 712; PMR($CDCl_3$): 0.94 (3H, *t*, $-CH_3$), 1.21-1.57 (6H, *m*, saturated methylenes), 1.9-2.28 (6H, *m*, allylic protons), 4.05 (2H, *d*, $-CH_2OH$), 5.38 (2H, *m*, $-C(H)=C(H)-$).

1-*Bromo*-(2*E*,7*Z*)-2,7-*dodecadiene*(*V*)

To a well cooled solution of IV (3.8 g) in dry ether

(100 ml), was added dry pyridine (2 drops) and PBr_3 (1 ml) in dry ether (10 ml) slowly with constant shaking. The reaction mixture was stirred for 2 hr at room temperature, refluxed for 2.5 hr, cooled and poured into ice-water. The ethereal layer was separated, washed with aq. $NaHCO_3$ (5%), water and dried. Removal of solvent afforded V (3.1 g, 78%), which was purified by column chromatography over silica gel using pet. ether as eluent.

16-*Tetrahydropranyloxy*-(5*Z*,10*E*)-5,10-*hexadecadiene* (*VI*)

To the cooled (−5°C) Grignard reagent prepared by treating 4-bromo-1-tetrahydropyranyloxybutane (3.0 g) in anhydrous THF (300 ml) with dry magnesium turnings (0.36 g) in anhydrous THF (3 ml) under N_2 atmosphere at room temperature followed by stirring at 30°C for 3 hr was added a solution of V (3.1 g) in dry THF during 15 min. The reaction mixture was stirred at −5° for another 30 min and to this was added catalytic amount of Li_2CuCl_4. The mixture was stirred further for 4 hr at −5° to −10° and left overnight. The reaction was quenched by the addition of saturated aq. NH_4Cl; extracted with ether, the ether layer separated and washed with water and dried. Removal of solvent and purification by chromatography afforded pure VI (1.8 g, 46%); IR: 2925, 2860, 1490, 1370, 1230, 1135, 1090, 1035, 1015, 970, 920, 875, 815 and 710; PMR($CDCl_3$): 0.95 (3H, *t*, $-CH_3$), 1.24-1.7 (18H, *m*, saturated methylenes), 2.0 (8H, *m*, allylic methylenes), 3.25-3.85 (4H, *m*, $-CH_2-O-\underset{|}{CH}-O-CH_2$), 4.58 (1H, *s*, $-O-\underset{|}{CH}-O-$), 5.02-5.52 (4H, *m*, olefinic protons).

(6*E*,11*Z*)-6,11-*Hexadecadien*-1-*ol* (*VII*)

To a solution of VI (1.8 g) in methanol (50 ml) was added PTS (500 mg), refluxed for 2 hr on a steam-bath, cooled and $NaHCO_3$ added till reaction ceased. The reaction mixture was filtered, the filtrate concentrated under reduced pressure, water added to the residue, extracted with ether and the ether layer washed with brine and dried. Removal of solvent afforded a residue which was chromatographed over neutral alumina to yield VII (0.89 g, 67%); IR: 3450, 1650, 1025, 965 and 760; PMR($CDCl_3$): 0.98 (3H, *t*, $-CH_3$), 1.3 (12H, *s*, saturated methylenes), 2.03 (8H, *m*, allylic methylenes), 3.6 (2H, *t*, $-CH_2OH$), 5.05-5.55 [4*H*, *m*, $(-CH=CH-)_2$].

(6*E*,11*Z*)-6,11-*Hexadecadien*-1-*yl acetate* (*I*)

The alcohol VII (0.89 g) was stirred with pyridine (1 ml) and acetic anhydride (2 ml) for 24 hr at room temperature usual work-up followed by purification of the residue over neutral alumina column afforded I (0.73 g, 70%); IR: 2920, 2860, 1730, 1650, 967, 1245, 967 and 707; PMR(CCl_4): 0.95 (3H, *t*, $-CH_3$), 1.28 (12H, *s*, saturated methylenes), 1.98 (11H, *m*, allylic methylenes and overlapped *s*, $-O-COCH_3$), 3.99 (2H, *t*, $-CH_2-OCO$), 4.95-5.42 (4H, *m*, allylic protons).

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Reported Formation of 3-Arylthiazolo-[2,3-*c*][1,2,4]triazepines in the Reaction of 2-Hydrazino-4-aryl-thiazoles with Pentane-2,4-dione: A Reinvestigation

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The condensation of 2-hydrazino-4-arylthiazoles (**1a-d**) with pentane-2, 4-dione (**6**) results in the formation of 2-(3′, 5′-dimethylpyrazol-1′-yl)-4-arylthiazoles (**2a-d**) and not the 3-arylthiazolo [2,3-*c*] [1,2,4] triazepines (**3**) as reported. The correct structural assignment is based on PMR, ^{13}CNMR and high resolution mass spectrometry of the products (**2a-d**). These products have been obtained by an alternate route involving phenacyl bromides (**4**) and 3, 5-dimethylpyrazol-1-thiocarboxamide (**5**).

Formation of pyrazoles (**2**) by the condensation of 2-hydrazinothiazoles (**1**) or 2-hydrazinobenzothiazoles and pentane-2, 4-dione (**6**) has recently been reported by us[1-3]. The structural assignment was based on the spectral data and on the belief that in all situations where a competitive five-membered ring closure can be envisaged, pyrazole formation should be a favoured process. However, two groups of workers[4,5] have independently assigned thiazolo [2, 3-*c*][1,2,4] triazepine structure (**3**) to the products obtained by the reaction of **1** and **6** under almost similar experimental conditions[4,5]. We present in this communication evidence to show that the structure (**3**) is in error and the products, in fact, have structure (**2**).

Thus, refluxing **1a-d** with **6** in either ethanol containing a few drops of acetic acid[1] or in gl. acetic acid[4,5] led to the formation of identical products as evidenced by their melting points and superimposable IR spectra. The most characteristic feature in the PMR spectra ($CDCl_3$) of the products was the appearance of sharp singlets at δ 2.3 (3H), 2.7 (3H) and 6.0 (1H) assignable to methyl groups located at positions 3 and 5 and to the pyrazole 4-H, respectively. These values are in complete agreement with the recorded values for several compounds having a 3, 5-dimethylpyrazole moiety[6]. Further support to the pyrazole structure was provided by the ^{13}CNMR spectra ($CDCl_3$) which displayed signals at about 150, 109 and 142 ppm, in excellent agreement with the values reported for the C-3, C-4 and C-5 carbons, respectively, of pyrazoles[7].

The mass spectra of these compounds have been studied by us[1] as well as by other workers[4,5] and the presence of a peak of high intensity at *m/z* 95 was recorded. Accurate mass measurements gave a value of *m/z* 95.0610 disclosing its elemental composition as $C_5H_7N_2$ (calc. *m/z* 95.0609), which corresponded to the 3, 5-dimethylpyrazole moiety. The most obvious route leading to the formation of this abundant ion is the simple cleavage of the two heterocyclic moieties involving C−N bond rupture in structure (**2**). However, this ion was erroneously shown to arise through a multistep complex process in order to accommodate a thiazolotriazepine structure (**3**)[4,5].

Structure (**2**) for the above compounds was finally established by synthesizing **2a-d** through an alternate route. Mixing an equimolar aqueous ethanolic solution of thiosemicarbazide hydrochloride and **6** resulted in the formation of 3, 5-dimethylpyrazole-1-thiocarboxamide (**5**) in 90% yield, m.p. 98° (lit.[8] m.p. 99°). PMR spectrum (in $CDCl_3$) of **5** displayed signals at δ 2.25, 2.65 and 6.0 in agreement with its pyrazole structure. Furthermore, prolonged refluxing of an ethanolic solution of **5** resulted in the formation of 3, 5-dimethylpyrazole, which displayed in its PMR spectrum in $CDCl_3$ a singlet (1H) at δ 6.1 and an expected six-proton singlet at δ 2.25 apparently due to tautomerism. When an ethanolic solution of **5** and an appropriate phenacyl bromide (**4a-d**) was refluxed for 3 hr, concentrated and cooled, a precipitate was deposited which on washing with dil. Na_2CO_3 solution and crystallization from ethanol furnished **2a-d** in 50-70% yield. The compounds **2a-d** were identical with those prepared through the condensation of **1** and **6** (m.p., m.m.p., PMR and superimposable IR spectra).

Finally, claims of obtaining seven-membered ring structures in preference to five-membered ring structures in the reaction of heterocyclic hydrazines and 1, 3-diketones need careful scrutiny. We have recently reassigned pyrazole structure[9] to the product obtained in the reaction of 2-hydrazinoquinoline and **6** as opposed to the 'diazepine' structure[10] and are currently investigating the structure of the product formulated as 'thiazolotriazepine' obtained by the condensation of 2-hydrazinonaphthothiazoles and **6**[11]

We are grateful to the CSIR and UGC, New Delhi for financial assistance, Chairman, Chemistry

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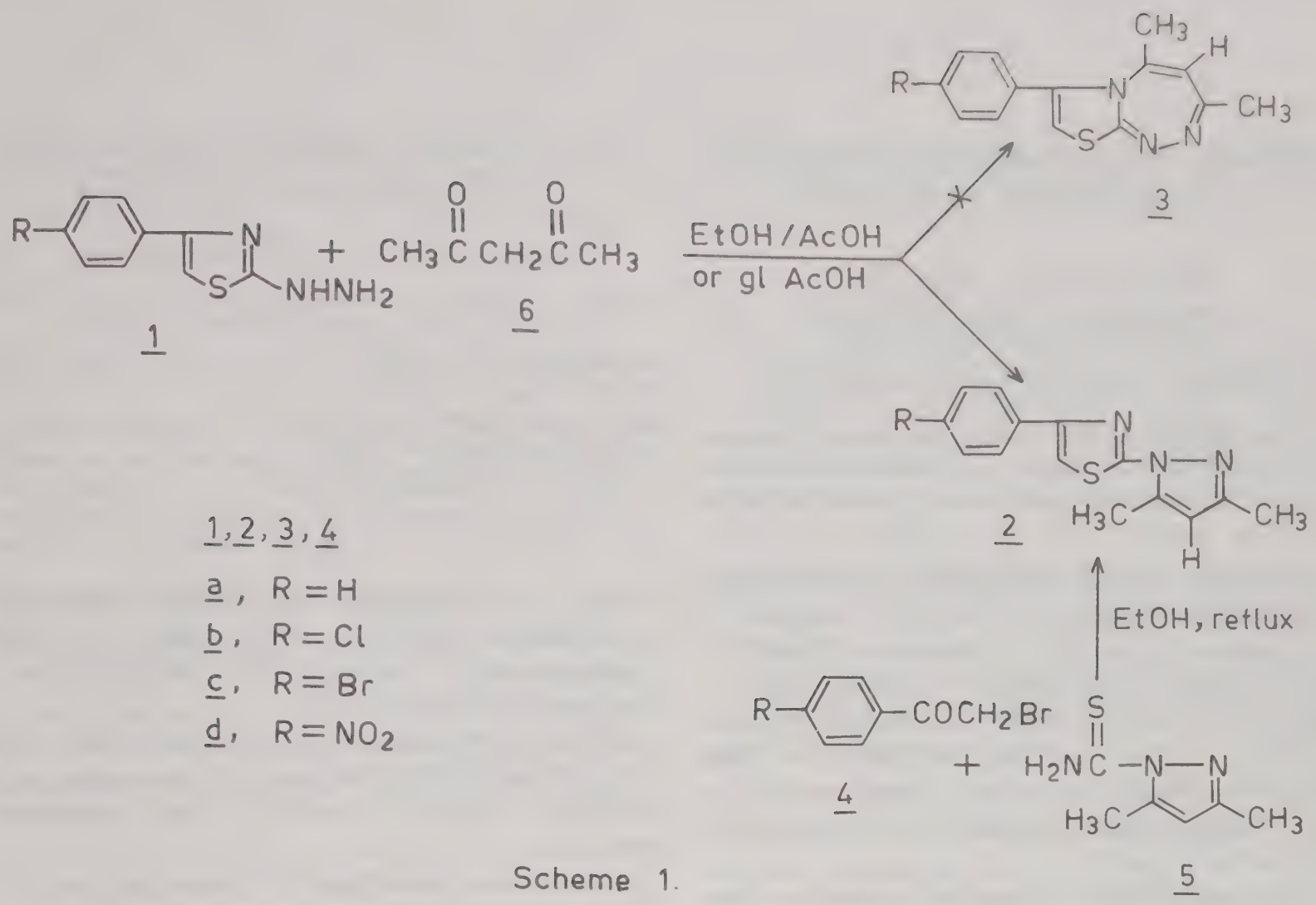

1, 2, 3, 4

a, R = H
b, R = Cl
c, R = Br
d, R = NO_2

Scheme 1.

Department, Kurukshetra University for providing facilities and to Dr P Traldi, Consiglio Naxionole delle Ricerche, Italy for running the mass spectra.

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One-step Conversion of Oxotetrahydrocarbazole into Carbazole

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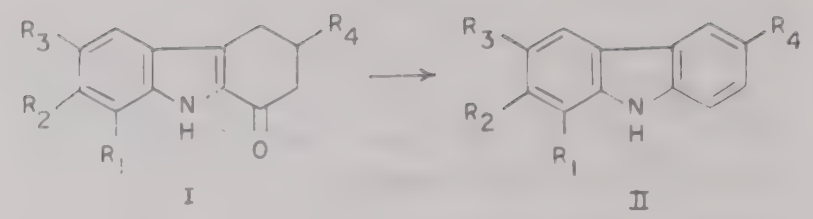
Oxotetrahydrocarbazoles (Ia-e) when heated with a 1:1 mixture of KOH + NaOH furnish the corresponding carbazoles (IIa-e) in good yields (~80%). The method appears to be of general applicability.



I II

(a) $R_1=R_2=R_3=R_4=H$.
(b) $R_1=CH_3$; $R_2=R_3=R_4=H$
(c) $R_1=R_3=R_4=H$; $R_2=CH_3$
(d) $R_1=R_2=R_4=H$; $R_3=CH_3$
(e) $R_1=R_2=H$; $R_3=OCH_3$; $R_4=CH_3$.

The reported method of converting oxotetrahydrocarbazole into carbazole via (a) reduction of oxotetrahydrocarbazole to tetrahydrocarbazole by Wolff-Kishner-Huang-Minlon reduction; and (b) dehydrogenation of tetrahydrocarbazole to carbazole by Pd/C, is time-consuming and yields are poor. Herein we report a one-step, simple method for converting oxotetrahydrocarbazole into carbazole in high yields.

Birch and White[1] converted α-tetralone into naphthalene by fusion with alkali. We thought that it could be utilised in the synthesis of carbazoles.

In a typical procedure oxotetrahydrocarbazole (I, 500 mg) was heated at 230° for 1 hr with a 1:1 mixture (100 mg) of sodium and potassium hydroxides. Carbazole (II) was sublimed on to the cooler part of the tube. It was removed and further purified by crystallisation and in some cases by column chromatography. Carbazole (IIa-e) were obtained in very good yields (~80%).

All the compounds were fully characterised by their UV, IR and PMR data and by comparison with authentic samples prepared by the conventional way[2-3].

The authors thank Prof B B Biswas and prof D P Chakraborty for their interest in the work.

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A One-Step Synthesis of Heterocyclic Imidazo[4,5-*b*]quinoxalines

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Synthesis of hetero[1′,2′:1,2]imidazo[4,5-*b*]quinoxalines **6**, **8** and **10** has been achieved by the fusion of 2-aminopyridine (**5**), 2-aminopyrimidine (**7**) and 2-aminobenzimidazole (**9**), respectively with 2,3-dichloroquinoxaline (**4**) in the presence of sodium acetate. The fluorescent properties of these compounds have been studied.

Imidazo[4,5-*b*]quinoxaline moiety fused to heterocyclic system is one of the interesting systems reported in the synthesis of cyanine dyes[1-6] and fungicides[7]. Recently, we have examined the reaction of thioamide with 2,3-dichloroquinoxaline in which the tautomeric form of thioamide takes part to produce thiazolo[4,5-*b*]quinoxalines[8].

To explore the synthetic potential of this type of condensation, we report here a single-step synthesis of some hetero[1′,2′:1,2]imidazo[4,5-*b*]quinoxalines involving fusion of 2,3-dichloroquinoxaline with 2-amino-1-N-heterocycles. The fused heterocyclic systems are interesting because of the increased conjugation and fluorescent properties, so the prepared heterocycles were also studied for their fluorescent properties.

Fusion of 2-aminopyridine (**5**), 2-aminopyrimidine (**7**) and 2-aminobenzimidazole (**9**) with 2,3-dichloroquinoxaline (**4**) in the presence of an acid-binding agent such as sodium acetate gave pyrido[1′,2′:1,2]imidazo-[4,5-*b*]quinoxaline (**8**) and 7*H*-benzimidazol[1′,2′:1,2]-imidazo[4,5-*b*]quinoxaline (**10**) respectively in fairly good yields. The key intermediate, 2,3-dichloroquinoxaline (**4**) was prepared from 1*H*,4*H*-quinoxaline-2,3-dione (**3**) which was obtained by the reaction of 1,2-diaminobenzene (**1**) with oxalic acid (2).

Fluorescent properties

The condensed imidazo[4,5-*b*]quinoxalines (**6**, **8** and **10**) were dark in colour and showed intense green fluorescence in daylight in most of the common organic solvents. The fluorescent properties of these compounds in DMF were examined and the results are given in Table 1. Compounds **6**, **8** and **11** absorb in UV-region ranging from 337 to 359 nm and show fluorescence emission maxima in the region 509 to 520 nm, and hence these compounds impart green fluorescence.

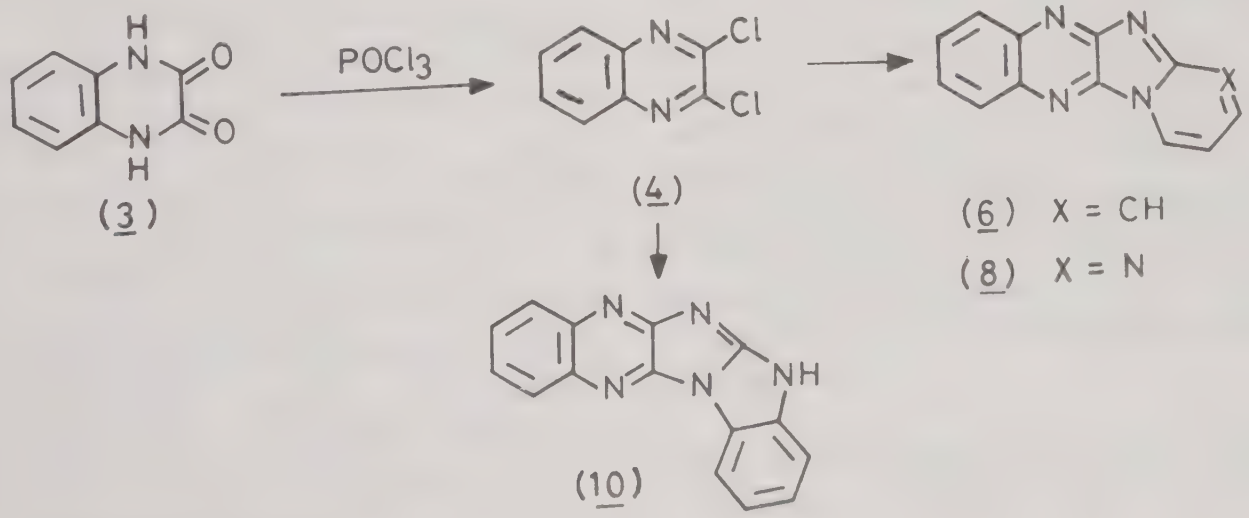
2-Aminobenzimidazole (**9**)[9], 1*H*,4*H*-quinoxaline-2,3-dione (**3**)[10] and 2,3-dichloroquinoxaline (**4**)[11] were prepared by known methods.

Pyrido[1′,2′:1,2]*imidazo*[4,5-*b*]*quinoxaline* (**6**)

A mixture of 2,3-dichloroquinoxaline (**4**; 1.99 g, 0.01 mol), 2-aminopyridine (**6**; 0.94 g, 0.01 mol) and sodium acetate (1.64 g, 0.02 mol) was heated in an oil-bath at 170-180° for 3 hr, cooled to room temperature and poured into ice-water (about 150 g). The solid obtained was filtered, dried and subjected to TLC using benzene-ethyl acetate (1:1) as irrigant when it showed a single fluorescent spot with R_f of about 0.7. The product was, therefore, purified by column chromatography over neutral alumina using benzene-ethyl acetate (1:1) as eluent, MS: *m/z* 220 (M^+).

Similarly, pyrimido[1′,2′:1,2]imidazo[4,5*b*]-quinoxaline (**8**, M^+ at *m/z* 221) and 7*H*-benzimidazo[1′,2′:1,2]imidazo[4,5-*b*]quinoxaline (**10**) were synthesised.

The characterization data of **6**, **8** and **10** are given in Table 1.



(3) (4) (6) X = CH (8) X = N (10)

Table I —Characterization Data and Absorption and Fluorescence Emission Spectra of Condensed Imidazo-[4,5-*b*]quinoxalines

Compd*	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.)			Absorption λ_{max} (nm)	Fluorescence Emission λ_{max} (nm)	log ε	Q mg
				C	H	N				
6	265	58	$C_{13}H_8N_4$	70.7 (70.9	3.4 3.6	25.3 25.4)	345	520	4.07	5.32
8	260	55	$C_{12}H_7N_5$	65.0 (65.1	3.0 3.1	31.5 31.6)	337	516	4.04	5.36
10	340	56	$C_{15}H_9N_5$	69.3 (69.5	3.4 3.4	26.8 27.0)	359	509	4.28	6.29

*All the compounds are dark brown in colour
ε, Molar extinction coefficient
Q, Quantity of compound dissolved in 100 ml solvent required for 100 units of intensity

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Reactions of 4-Anilinomethylene- & 4-Ethoxymethylene-2-phenyl-2-oxazolin-5-ones

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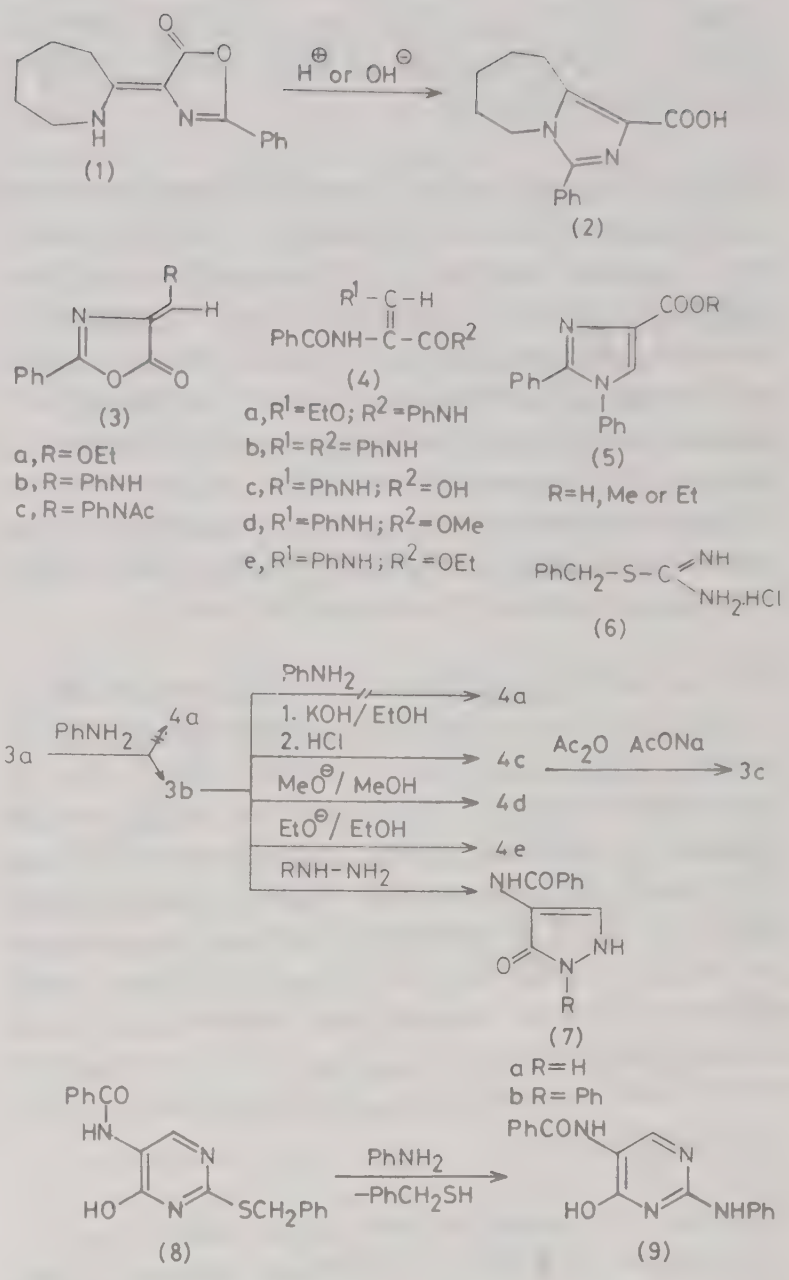
4-Anilinomethylene-2-phenyl-2-oxazolin-5-one (**3b**) is resistant to aminolysis with aniline. However, it undergoes facile hydrolysis and alcoholysis, and affords pyrazolones (**7**) on reaction with hydrazines. 4-Ethyoxymethylene-2-phenyl-2-oxazolin-5-one (**3a**) gives **3b** and 5-benzamido-2-benzylthio-4-hydroxypyrimidine (**8**) with aniline and S-benzylisothiouronium hydrochloride respectively. Compound **8** when heated with aniline, is converted into 2-anilino-5-benzamido-4-hydroxypyrimidine (**9**).

Hydrolysis of 4-(hexahydrozepin-2-ylidene)-2-phenyl-2-oxazolin-5-one (**1**) and subsequent cyclisation of the product into **2** are known in the literature[1], but similar studies with 4-aminomethylene-2-oxazolin-5-ones do not seem to have been carried out. In this note we report the results of our investigation on 4-anilinomethylene-2-phenyl-2-oxazolin-5-one (**3b**)[2,3] with several nucleophiles and attempted cyclisation of the products. We have found that **3b** undergoes facile hydrolysis and base-catalysed alcoholysis, but its aminolysis with aniline does not occur. Attempt to cyclise **4c-e** to **5** in boiling glacial acetic acid was also unsucessful. It is noteworthy that the ester **4e** remained unaffected, even on heating at 250° in liquid paraffin, and did not undergo Conrad-Limpach reaction to give quinoline derivative. The acid **4c**, however, afforded the acetyl derivative (**3c**) with acetic anhydride. The reaction of **3b** with hydrazines gave pyrazolones (**7**). This can be explained by invoking the imine-form of the enamine (**3b**) which would undergo exchange of the anilino moiety followed by intramolecular cleavage of the 1,5-bond by hydrazine. The reaction of the 1,3-binucleophile (**6**) with **3b** was also examined in this connection. A sulphur containing product was obtained which did not give proper elemental analysis corresponding to 5-benzamido-2-benzylthio-4-hydroxypyrimidine (**8**) which was alternatively prepared by the interaction of **3a** and **6**. Though **8** was stable in hot sodium hydroxide solution, it afforded 2-anilino-5-benzamido-4-hydroxypyrimidine (**9**) on heating with aniline.

The compounds reported were characterised by spectral data and elemental analyses.



All melting points are uncorrected. The IR and PMR spectra were recorded on Perkin Elmer 720 and Jeol 90 spectrophotometers respectively.

2-Benzamido-3-phenylamino-2-propenoic acid (**4c**)

Compound **3b** (0.26 g; 0.001 mol) in ethanol (10 ml) containing KOH (0.07 g; 0.0012 mol), was heated under reflux for 0.5 hr. The solution was stripped of solvent *in vacuo* and the residue treated with distilled water, filtered, and washed. The filtrate and washings were combined and acidified with conc. HCl to give **4c**, yield 0.13 g (46%), m.p. 176-78°. It could not be recrystallised and did not give proper elemental analysis. However, it afforded 4-N-acetylanilino-methylene-2-phenyl-2-oxazolin-5-one (**3c**)[3] m.p. 156-57°, on heating with acetic anhydride and freshly fused sodium acetate.

Ethyl 3-anilino-2-benzamido-2-propeonate (**4e**)

A solution of **3b** (0.26 g; 0.001 mol) in ethanol (10 ml)

containing KOH (0.01 g) was heated under reflux for 0.5 hr, concentrated to dryness *in vacuo* and the residue treated with distilled water (8 ml) to afford a solid which was filtered, washed and recrystallised from aq. ethanol, yield 0.25 g (80%), m.p. 148-50° (Found: C, 67.4; H, 5.6; N, 8.6. $C_{18}H_{18}N_2O_3.0.5\ H_2O$ requires C, 67.4; H, 6.0; N, 8.8%).

4-Benzamido-3-pyrazolin-5-ones (**7**): *General procedure*

A mixture of **3b** and hydrazine or phenylhydrazine in 1 : 1.1 molar ratio was heated under reflux in ethanol (70 ml/g of **3b**) for 4 hr. The solution was stripped of solvent *in vacuo* and the residue washed with pet. ether. In the case of **7b** the residue was triturated with benzene and recrystallised from benzene. However, in the case of pyrazolin-5-one (**7a**) the residue was triturated with water, and only after seeding and long standing, the product was recrystallised from water. The physical data of **7** are given in Table 1.

5-Benzamido-2-benzylthio-4-hydroxypyrimidine (**8**)

To a mixture of 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (**3a**; 0.43 g; 0.002 mol) and S-benzylisothiouronium chloride (**6**; 0.41 g; 0.002 mol) in ethanol (15 ml), was added triethylamine (0.56 ml; 0.004 mol), and the reaction mixture heated under reflux for 1 hr. The solvent was removed *in vacuo* and the residue treated with aq. ethanol to give a solid which was filtered, washed and recrystallised from ethanol, yield 0.48 g (74%); m.p. 251-53° (Found: C, 64.3; H, 4.8; N, 12.4. $C_{18}H_{15}N_3O_2S$ requires C, 64.1; H, 4.5; N, 12.5%).

2-Anilino-5-benzamido-4-hydroxypyrimidine (**9**)

A mixture of **8** (0.1g; 0.0003 mol), aniline (0.1 ml; 0.0011 mol) and glacial acetic acid (0.5 ml) was heated in an oil-bath at 170° for 1 hr, cooled, treated with ethanol, filtered and recrystallised from ethanol, yield 0.09 (98%); m.p. 295-97°. (Found: C, 66.5; H, 4.6; N, 18.0. $C_{17}H_{14}N_4O_2$ requires C, 66.7; H, 4.6; N, 18.3%).

We are thankful to CSIR, New Delhi for the award of a senior fellowship to one of us (P K T).

Table 1 – Characterization Data of Various Compounds Prepared

Compd	Yield (%)	m.p. °C	PMR ($CDCl_3$/TMS) δ(ppm)
3c[a]	46	156-57	2.06(*s*, 3H, CH_3CO-), 7.09-7.56(*m*, 10H, Ar–*H*), 8.21(*s*, 1H, 4-C=CH).
4c[b]	46	176-78	f
4d[c]	91	178-79	3.81(*s*, 3H, CH_3), 7.0(*d*, 1H, C=C*H*–NHPh), 7.15-7.9(*m*, 10H, Ar–*H*), 8.29(*s*, 1H, PhCON*H*–), 8.88(*d*, 1H, =CH–N*H*Ph).
4e[d]	80	148-50	1.36(*t*, 3H, $-CH_2-CH_3$), 4.26(*q*, 2H, CH_2-CH_3), 7.0(*d*, 1H, C=C*H*–NHPh), 7.15-7.9(*m*, 10H, Ar–*H*), 8.29(*s*, 1H, PhCON*H*), 8.89(*d*, 1H, =CH–N*H*–Ph).
7a[e]	70	205-6	f
7b[e]	86	198-99	7.12-7.81(*m*, 12H, 3-CH, 2-NH and Ar*H*), 7.93(*s*, 1H, CONH).
8[d]	74	251-53	f
9[d]	98	295-97	f

[a] Identical with the product[3] obtained by acetylation of **3b**.
[b] Could not be prepared analytically pure. On cyclisation with acetic anhydride and fused sodium acetate it afforded **3c**.
[c] In the literature it was prepared by the reaction of aniline and methyl 3-chloro-2-benzamidoacrylate[4].
[d] For elemental analysis see text.
[e] Identical with the product prepared by the literature method[3].
[f] Insufficiently soluble in $CDCl_3$.

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Synthesis of β-Lactams Through the Use of Mixed Carboxylic-Sulphonic Acid Anhydrides

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Use of mixed carboxylic-sulphonic acid anhydrides for the synthesis of a variety of simple and fused β-lactams (I-IV, VI and VII) is described.

The imine-ketene cycloaddition reaction is a versatile route to recemic β-lactams. In a recent communication[1], we concluded that such a cycloaddition reaction is non-concerted and therefore, often yields a mixture of both *cis*- and *trans*-isomers. Annelation of the imine, to produce a β-lactam, can be carried out by reacting it with appropriate activated acid derivatives. Use of mixed anhydrides for the synthesis of 2-azetidinones has already been amply demonstrated[2,3].

We have further modified this method which involves the use of mixed carboxylic-sulphonic acid anhydrides. The anhydride (II) can be prepared *in situ* by stirring a mixture of an alkoxy/aryloxy/arylacetic acid, Et_3N and alkyl/arylsulphonyl chloride in CH_2Cl_2 at 0-5° for 30 min. The schiff base in CH_2Cl_2 is then added dropwise and stirred overnight. Usual work-up of the reaction mixture produced the crude β-lactams (Ia-i) which were purified by column chromatography and recrystallisation.

As anticipated, the yields of the β-lactams formed through the use of benzenesulphonyl chloride were better than through methanesulphonyl chloride. The former provides a better leaving group than the latter. PMR studies of the 2-azetidinones reported herein (Table 1) reveal that the reaction is stereoselective. The orientation (*cis*- or *trans*-) of the C-3 and C-4 protons seems to depend upon the nature of the acid as well as the imine component used in the preparation of a particular β-lactam.

Formation of the azacepham (III) and the carbacepham (IV) analogs in high yield from the appropriate cyclic imines[4,5] further demonstrates the scope of this method. The reaction with cyclic imines is also stereoselective and only single isomers of the β-lactams are produced.

It is believed that the presence of a free carboxy group in the β-lactam molecule is essential for antibiotic activity[6]. To introduce this function in the equilenin-type β-lactams, the imine V was prepared[7] by acylating 2-(1-naphthyl)ethylamine with ethoxalyl chloride[8] followed by Bischler-napieralski cyclization. Reaction of V with phenoxyacetic acid using the above method yielded the equilenin-type ester β-lactam (VI) in 65% yield. The IR spectrum of this compound exhibited characteristic bands at 1770 (β-lactam CO) and 1740 cm^{-1} (ester CO). This structure got further support from its PMR spectrum (*vide infra*).

Conversion to the carboxy-β-lactam (VII) was accomplished in 40% yield by hydrolysing[9] the ester β-lactam VI with 0.1N aq. NaOH in acetone. That the β-lactam ring remained intact was confirmed by the IR spectrum of this compound showing peaks at 1740 (β-lactam CO) and 1710 cm^{-1} (acid CO). The peak at 1710 cm^{-1} disappeared on adding a drop of morpholine (test for an acid function).

All melting points reported are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded in nujol mull on a Perkin-Elmer 337 spectrophotometer and PMR spectra in $CDCl_3$ on a Varian EM-390 90 MHz instrument using TMS as internal standard (chemical shifts in δ, ppm). Organic extracts were dried over anhyd. sodium sulphate.

1-(p-Methoxyphenyl)-3-phenoxy-4-(3',4'-methylenedioxyphenyl)-azetidin-2-one (Ia)

A solution of phenoxyacetic acid (1.52 g, 0.01 mol), benzene/methanesulphonyl chloride (1.77/1.145 g, 0.01 mol) and Et_3N (2.02 g, 0.02 mol) in anhyd. dichloromethane (100 ml) was stirred at 5° for 30 min. A solution of imine from piperonal and *p*-anisidine (2.55 g, 0.01 mol) in dry CH_2Cl_2 (50 ml) was then added dropwise at low temperature. The reaction mixture was stirred overnight. The resulting solution was washed with 5% $NaHCO_3$ solution, water and dried. Removal of solvent provided the title compound (Ia) in 60% yield, which was purified by column chromatography and recrystallised from ethanol, m.p. 181-82 (lit.[2], m.p. 181-82°).

Monocyclic β-lactams (Ib-i) and bicyclic β-lactams (III and IV) were similarly prepared by using alkoxy/aryloxy/arylacetic acid, benzenesulphonyl chloride, Et_3N and appropriate schiff bases. Recrystallisation from ethanol provided the pure β-lactams in high yields. Physical data of these compounds are given in Table 1.

4-Carbethoxy-1,2-dihydrobenz[f]isoquinoline (V)

It was prepared according to the reported procedure[7].

Table 1—Characterisation Data of Various β-Lactams Prepared

Compd	m.p. °C	Yield (%)	Mol. Formula	Found (%) (Calc.) C	H	N	Spectral data
Ib	174-76	60	$C_{23}H_{17}NO_5Cl_2$	60.2 (60.3	3.6 3.7	2.8 3.0)	IR: 1750 (β-lactam CO). PMR: 3.85 (*s*, 3H, $-OCH_3$), 5.35 (*d*, 1H, C_4-H, J = 5.0 Hz), 5.5 (*d*, 1H, C_3-H, J = 5.0 Hz), 6.0 (*s*, 2H, $-OCH_2O-$) and 6.8-7.6 (*m*, 10H, Ar-*H*).
Ic	150-52	58	$C_{23}H_{19}NO_4$	73.8 (74.0	5.0 5.1	3.6 3.7)	IR: 1740 (β-lactam CO). PMR: 3.83 (*s*, 3H, $-OCH_3$), 4.3 (*d*, 1H, C_4-H, J = 2.5 Hz), 4.85 (*d*, 1H, C_3-H, J = 2.5 Hz), 6.05 (*s*, 2H, $-OCH_2O-$) and 6.85-7.6 (*m*, 12H, Ar-*H*).
Id	165-67	60	$C_{19}H_{19}NO_5$	66.7 (66.9	5.5 5.6	3.9 4.1)	IR: 1740 (β-lactam CO). PMR: 0.95 (*t*, 3H, $-CH_2CH_3$), 3.15-3.65 (*m*, 2H, $-CH_2CH_3$), 3.8 (*s*, 3H, $-OCH_3$), 4.9 (*d*, 1H, C_4-H, J = 5.0 Hz), 5.1 (*d*, 1H, C_3-H, J = 5.0 Hz), 6.0 (*s*, 2H, $-OCH_2O-$) and 6.8-7.5 (*m*, 7H, Ar-*H*).
Ie	130-32	50	$C_{23}H_{19}NO_3$	77.2 (77.3	5.1 5.3	3.7 3.9)	IR: 1750 (β-lactam CO). PMR: 2.3 (*s*, 3H, $-CH_3$), 4.25 (*d*, 1H, C_4-H, J = 2.5 Hz), 4.9 (*d*, 1H, C_3-H, J = 2.5 Hz), 6.05 (*s*, 2H, $-OCH_2O-$) and 6.95-7.65 (*m*, 12H, Ar-*H*).
If	80-82	50	$C_{25}H_{23}NO_5$	71.7 (71.9	5.3 5.5	3.3 3.4)	IR: 1750 (β-lactam CO). PMR: 2.3 (*s*, 3H, $-CH_3$), 3.95 (*s*, 6H, 2 × $-OCH_3$), 4.25 (*d*, 1H, C_4-H, J = 2.5 Hz), 4.85 (*d*, 1H, C_3-H, J = 2.5 Hz), 6.0 (*s*, 2H, $-OCH_2O-$) and 6.85-7.5 (*m*, 10H, Ar-*H*).
Ig	163-65	50	$C_{22}H_{16}N_2O_5Cl$	57.4 (57.5	3.4 3.5	6.0 6.1)	IR: 1755 (β-lactam CO). PMR: 3.95 (*s*, 3H, $-OCH_3$), 5.15 (*d*, 1H, C_4-H, J = 2.5 Hz), 5.2 (*d*, 1H, C_3-H, J = 2.5 Hz) and 6.95-8.4 (*m*, 11H, Ar-*H*).
Ih	180-82	55	$C_{22}H_{18}N_2O_5$	67.6 (67.7	4.5 4.6	7.0 7.2)	IR: 1755 (β-lactam Co). PMR: 3.95 (*s*, 3H, $-OCH_3$), 5.1 (*d*, 1H, C_4-H, J = 2.0 Hz), 5.25 (*d*, 1H, C_3-H, J = 2.0 Hz) and 6.9-8.4 (*m*, 13H, Ar-*H*).
Ii	109-110 (lit.[2] 110-11)	—	—	—	—	—	—
III	115-16 (lit[10] 115-16)	—	—	—	—	—	—
IV	63-64*	45	$C_{24}H_{19}O_3NCl_2$	65.4 (65.5	4.1 4.3	3.0 3.2)	IR: 1760 (β-lactam Co). PMR: 2.83 (*t*, 2H, benzylic CH_2-), 3.75 (*t*, 2H, $-NCH_2-$), 3.9 (*s*, 3H, $-OCH_3$), 5.45 (*s*, 1H, C_7-H) and 6.9-7.7 (*m*, 11H, Ar-*H*).

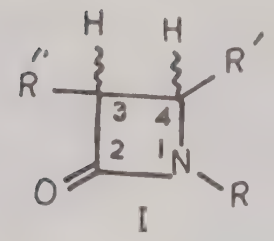
*Recrystallised from CCl_4.

3-*Deoxy*-13-*aza*-14-*carbethoxy*-15-*phenoxy*-16-*norequilenin* (*VI*)

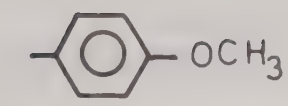
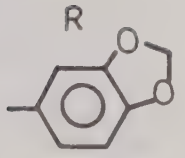
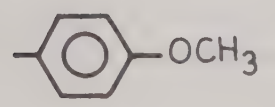
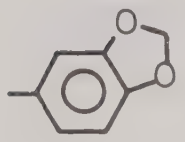
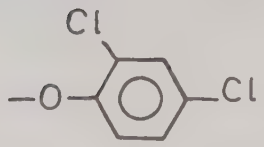
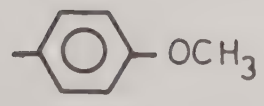
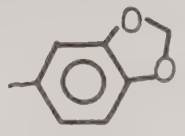
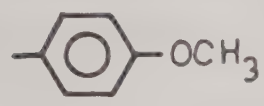
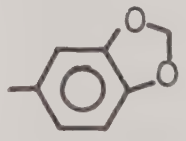
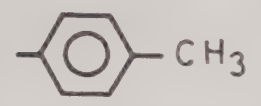
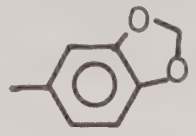
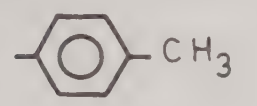
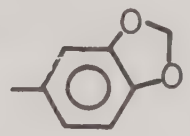
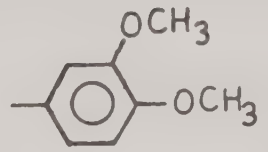
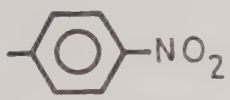
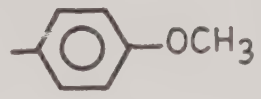
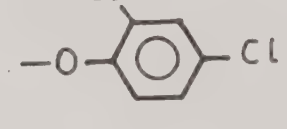
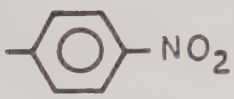
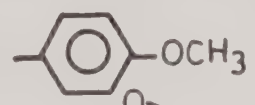
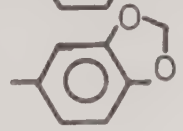
This β-lactam (VI) was prepared by annelating the imine V with phenoxyacetic acid using benzenesulphonyl chloride in the presence of Et_3N in CH_2Cl_2 by the procedure described for Ia. Recrystallisation from EtOH afforded the title compound in 65% yield, m.p. 114-16 ; IR: 1770 (β-lactam Co) and 1740 (ester Co); PMR: 1.25 (*t*, 3H, J = 7.0 Hz, $-COOCH_2CH_3$), 3.2-3.9 (*m*, 4H, $-N-CH_2-$ and benzylic $-CH_2-$), 4.25 (*q*, 2H, J = 7.0 Hz, $-COOCH_2-$), 5.35 (*s*, 1H, C_{15}-H) and 7.15-7.95 (*m*, 11H, Ar-*H*) (Found: C, 74.2; H, 5.3; N, 3.6. $C_{24}H_{21}NO_4$ requires C, 74.4; H, 5.4; N, 3.6%).

3-*Deoxy*-13-*aza*-14-*carboxy*-15-*phenoxy*-16-*norequilenin* (*VII*)

A solution of VI (3.87 g, 0.01 mol) in acetone (120 ml) and NaOH (100 ml, 0.01 *N* aq.) was heated on a water-bath for 1 hr. The reaction mixture was cooled, diluted with water and extracted with dichloromethane (2 × 50 ml) to remove any unreacted ester. The aq. layer was then acidified with dil. HCl and concentrated to remove acetone. On cooling, the separated solid

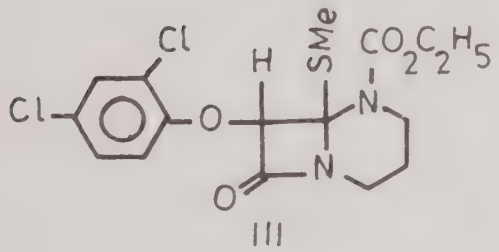


I

	R	R′	R″	C_3- & C_4-Hydrogens
(a)			-OPh	cis
(b)				cis
(c)			- Ph	trans
(d)			$-OC_2H_5$	cis
(e)			- Ph	trans
(f)				trans
(g)				trans
(h)			- OPh	trans
(i)	$-CH_2Ph$		- OPh	cis

$$RO-CH_2-\overset{O}{\overset{\|}{C}}-OSO_2R \quad ; \quad R = \text{alkyl, aryl}$$

II



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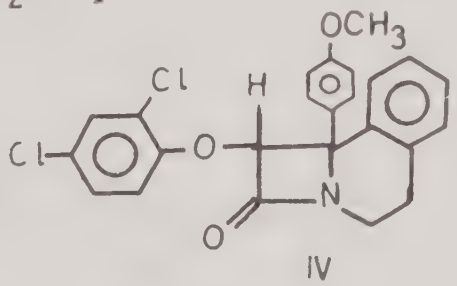

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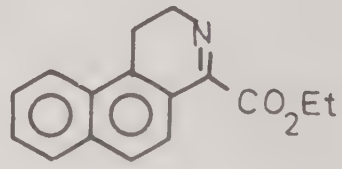

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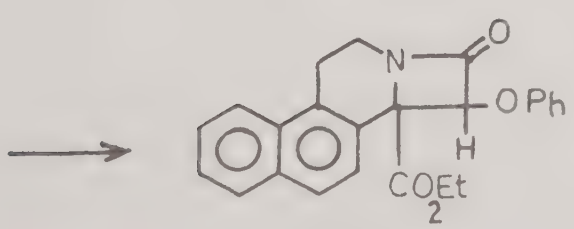

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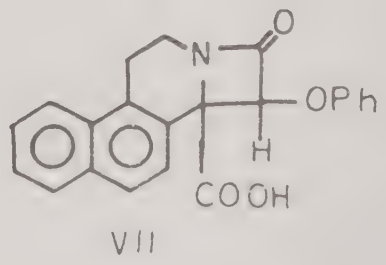

VII

product was filtered and recrystallised from CH_2Cl_2 – and pet. ether, yield 40%, m.p. 149-50 : IR: 1740 (β-lactam CO) and 1710 (acid CO, ascertained with a drop of morpholine) (Found: C, 73.4; H, 4.7; N, 3.7. $C_{22}H_{17}NO_4$ requires C, 73.5; H, 4.7; N, 3.9%).

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Synthesis of Heterocyclic Compounds via Ferrocene

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Heterocyclic derivatives of ferrocene such as methiodides of α-pyridylferrocene (**3**) and 3,4-dihydro-1-methylpyrido[3,4-*b*]ferrocene (**5**) have been prepared. These compounds on photolysis give 1-methyl-2-cyclopentadienylidene-1,2-dihydropyridine (**1**) and 1,2-dimethyl-3,4-dihydro-2*H*-cyclopenta[*c*]pyridine (**2**).

In the present work a simple and convenient method for the synthesis of 1-methyl-2-cyclopentadienyl-1,2-dihydropyridine (**1**) and 1,2-dimethyl-3,4-dihydro-2*H*-cyclopenta[*c*]pyridine (**2**) is reported. The known ferrocene intermediates (**3**) and (**5**) on photolysis afford **1** and **2** respectively in good yields without any isolation and purification problems.

The pronounced high reactivity of ferrocene allows the cyclopentadienyl (Cp) to act as a stable intermediate in many synthetic routes[1-3]. Pauson *et al.*[4] and Nesmeyanov[5] have reported series of heterocyclic derivatives of ferrocene and have proved their successful intermediacy in the synthesis of heterocyclic compounds.

The highly aromatic character of Cp rings of ferrocene has been used to introduce heterocyclic rings in the ferrocene system. Compounds, such as **3**, **4** and **5** were synthesised and further photolysed to give new metal-free heterocycles which were otherwise difficult to synthesise by conventional methods.

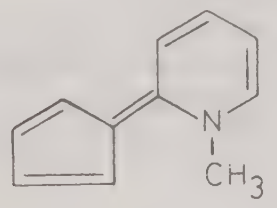
It is already known that Fe−C π-bond is weak. However, photolysis is found to be facile to cleave this bond. The method of Trifan and Nicholas[6] for cleaving this bond by reductive degradation using solutions of alkali metals in amines, is rather slow and less effective.

Photolyissis was carried-out in an alkaline medium and the mechanism probably involves photoreductive degradation of ferrocenyl group followed by the decomposition (Scheme 1). It is also found that photolysis occurs in those complexes which have a positive charge alpha to the ferrocenyl group.

The structure of the photolysed iron-free heterocycles thus obtained were confirmed by their analytical IR, PMR and mass spectral data.

Methiodide (**3**) *of α-pyridylferrocene*

α-Pyridylferrocene (2.6 g, 0.006 mol) prepared according to the method of Nesmeyanov[5] was dissolved in methyliodide (6 ml) and left for 5 days at room temperature. A red precipitate was formed which was filtered off and washed several times with ether, yield 1.82 g. The crude product was dissolved in ethanol (7 ml), filtered and precipitated with ether, yielding 1.40 g of methiodide (**3**). IR(KCl): 2920, 1610, 1510, 1375 cm^{-1} (Found: C, 47.8; H, 4.1; N, 3.3. $C_{16}H_{16}FeIN$ requires C, 47.4; H, 3.9; N, 3.4%).



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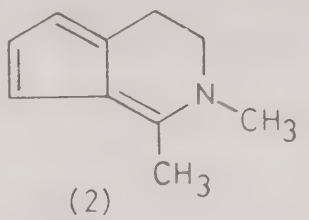

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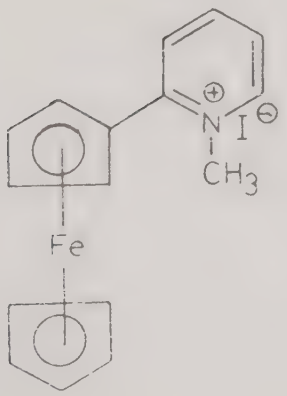

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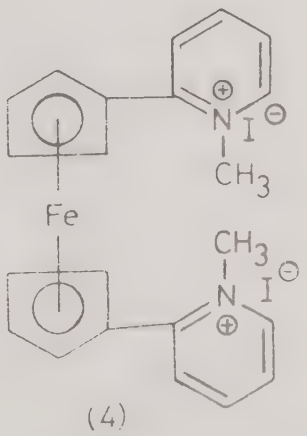

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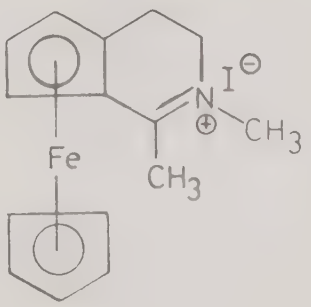
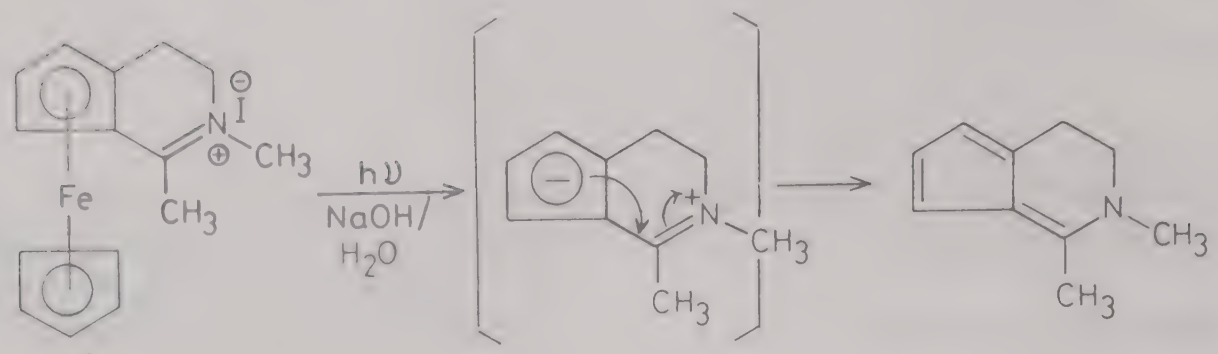


(5)



(5)

Scheme 1

Photolysis of methiodide (**3**): *Formation of N-methyl-2-cyclopentadienylidene-1,2-dihydropyridine* (**1**)

The methiodide (**3**) (1 g, 0.002 mol) was dissolved in water (5 ml) and 10% aq NaOH (20 ml) added to it. The mixture was irradiated under N_2 atmosphere with low pressure mercury lamp (RPM-Module, the Southern New England UV Co.) in a quartz equipment for 6 hr. During this period colour of the solution changed from deep-red to orange. A black residue was also formed which indicated that the reaction had taken place. The rection mixture was filtered, the filtrate extracted with ether, the ether extract washed with a small quantity of water, followed by 10% H_2SO_4 when both the aqueous acidic and ethereal layers became colourless.

When the acidic layer was made alkaline with 10% aq NaOH, an orange oil was obtained which was extracted into toluene and the extract evaporated *in vacuo* under N_2 atmosphere. An orange-yellow metal-free product (650 mg) was obtained which crystallized from hexane to afford **1**, yield 650 mg; IR(KCl): 1625, 1550, 1520, 1340, 1180 cm^{-1}; PMR($CDCl_3$): δ 3.85 (*s*, 3H, $N-CH_3$), 6.3-6.4 (*q*, 3H, H-6,9,5), 6.55 (*t*, 2H, H-7,8), 7.1 (*d*, 2H, H-3,4), 7.65 (*d*, 1H, H-2).

Methiodide (**5**) *of 3,4-dihydro-1-methylpyrido-[3,4-b]ferrocene*

To a solution of 3,4-dihydro-1-methylpyrido[3,4-*b*]ferrocene[5] (6 g, 0.023 mol) in toluene (80 ml) was added a solution of methyl iodide sufficient to precipitate the methiodide (**5**). The precipitate were filtered and crystallized from methanol, yield 3.8 g (52%); IR(KCl): 3310, 1420, 1220 cm^{-1} (Found: C, 46.0; H, 5.2; N, 4.0. $C_{15}H_8FeIN$ requires C, 45.6; H, 4.6; N, 3.6%).

Photolysis of methiodide (**5**): *Formation of 1,2-dimethyl-3,4-dihydro-2H-cyclopenta-[c]pyridine* (**2**)

The methiodide (**5**) (1 g, 0.0024 mol) was photolysed following the method adopted in the case of **3**. The yield of the metal-free product (**2**) obtained was 30 mg (30%); IR(KCl): 1610, 1480, 1820 cm^{-1}; PMR($CDCl_3$): δ 2.3 (*s*, 3H, CH_3), 2.75 (*t*, 2H, $CpCH_2$), 3.1 (*s*, 3H, $N-CH_3$), 3.3 (*t*, 2H, CH_2), 5.9 (*s*, 1H, H-5), 6.2 (*dd*, 2H, H-6,7) (Found: C, 77.4; H, 8.5; N, 6.7. $C_{10}H_{13}N$ requires C, 81.5; H, 8.9; N, 6.7%); MS: *m/z* 147.1841 (required for $C_{10}H_{13}N$, 147.2104). The peaks at *m/z* 132.0013, 65.0410 and 56.0511 corresponded to the loss of $-CH_3$, $-C_2H_5$ and $-CH_3N$, respectively.

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Studies on a New Phosphonate Carbanion

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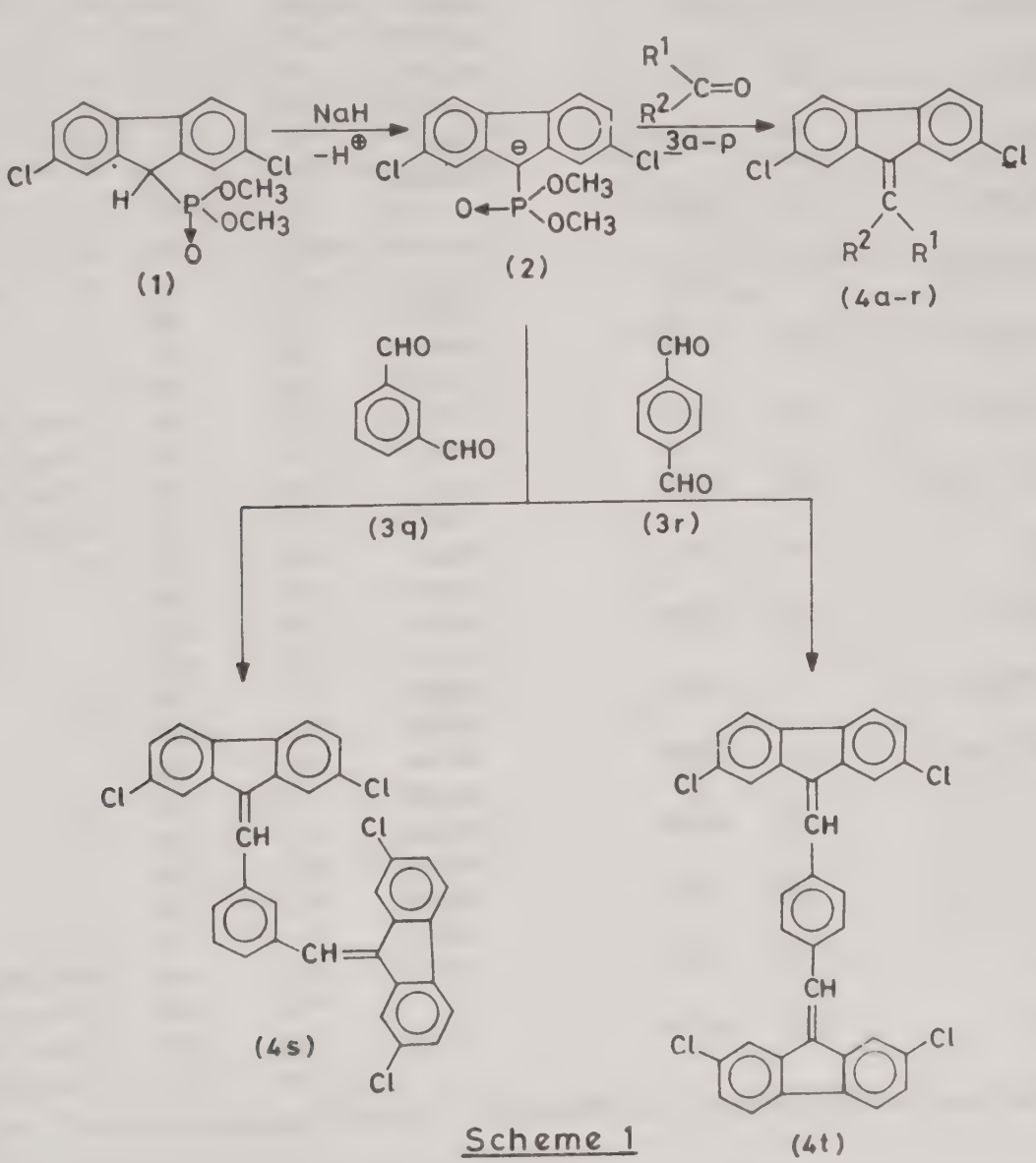
A new dimethyl 2,7-dichloro-9-fluorenyl phosphonate carbanion (**2**) has been generated and reacted with a series of aromatic aldehydes to give 9-arylidene-2,7-dichlorofluorenes (**4a-r**) in good yields. The reaction of **2** with isophthalaldehyde and terephthalaldehyde give 1,3-bis(2.7-dichloro-9-fluorenylidene)xylene (**4t**), respectively. The structural assignments of the phosphonate (**1**) and the resulting products are based on spectral data. The phosphonate shows a good antibacterial activity in soil.

Phosphonate carbanions are found to be good olefinating agents than the analogous phosphonium ylides and afford products in better yields[1-5]. Prompted by this and in continuation of our studies on the reactivity of phosphorous containing carbanions[6-9], we report here the reactivity of a new dimethyl 2,7-dichloro-9-fluorenylphosphonate carbanion (**2**) towards various mono and disubstituted benzaldehydes.

The reaction of trimethyl phosphite with 2,7-dichloro-9-bromofluorene at 150° gave dimethyl 2,7-dichloro-9-fluorenylphosphonate (**1**) in 70% yield. Treatment of **1** with NaH in THF produced a pinkish red colouration indicating the formation of phosphonate carbanion (**2**).

The reaction of **2** with a series of substituted benzaldehydes (**3a-p**) was carried out at 100° to afford 2,7-dichloro-9-(substituted benzylidene)fluorenes (**4a-r**) in 70-90% yields. A similar reaction of **2** with isophthalaldehyde and terephthalaldehyde gave 1,3-bis(2,7-dichloro-9-fluorenylidene)xylene(**4s**) and 1,4-bis(2,7-dichloro-9-fluorenylidene)xylene (**4t**) in 55-60% yields. The carbanion **2** also reacted with acetone and acetophenone to afford 2,7-dichloro-9-isopropylidene fluorene(**4u**) and 2,7-dichloro-9-(α-methylbenzylidene)fluorene(**4v**), respectively.



Scheme 1

The carbanion **2** was found to be more reactive than the phosphonium ylide[10]. It reacted smoothly with ketones unlike the corresponding phosphonium ylide[10]. The enhanced nucleophilicity of **2** was attributed to the inducive effect of $(CH_3O)_2P=O$ group. The phosphonate carbanion **2** was also found to be more reactive than dimethyl 9-fluorenyl-phosphonate[11].

All the fluorenes (**4a-v**) synthesized gave satisfactory elemental analyses and spectral data. The melting points were in accordance with those reported in literature[12]. The IR spectra of **4a-v** exhibited characteristic absorption bands at 1630-1590 (C=C) and 990-960 (out-of-plane deformation of C−H of CH=C system). In the PMR($CDCl_3$) spectra of **4** the olefinic protons appeared at δ 6.55-7.25, the aromatic protons as a multiplet at 6.55-8.35 and the aliphatic methyl and methoxy protons at 2.25 and 3.95, respectively.

The soil bacterial population was developed using Thornton's Agar media. The phosphonate **1** was tested on soil bacterial population using different con-

Table 1—Physical Data of Fluorene Derivatives (**4**)

Compd*	R_1	R_2	Yield (%)	Recrystallized from	m.p. (lit, m.p.) °C	Found (%) (Calc.) C	H	PMR($CDCl_3$) (δ, ppm)
4a	H	C_6H_5	65	AcOH	92-93	74.2	3.7	—
					(94-95)[12]	(74.3	3.7)	
4b	H	2-$CH_3C_6H_4$	90	$CHCl_3$	140-42	74.7	3.1	2.35 (*s*, 3H, CH_3),
					(142-43)[12]	(74.8	3.2)	7.25-8.30 (*m*, 11H, Ar-*H*)
4c	H	3-$CH_3C_6H_4$	67	$CHCl_3$	95-97	74.7	3.2	2.32 (*s*, 3H, CH_3),
					(96-97)[12]	(74.8	3.2)	7.20-8.35 (*m*, 11H, Ar-*H*)
4d	H	4-$CH_3C_6H_4$	70	EtOH	145-47	74.8	3.1	2.42 (*s*, 3H, CH_3),
					(148)[12]	(74.8	3.2)	7.28-8.35 (*m*, 11H, Ar-*H*)
4e	H	2-ClC_6H_4	50	AcOH	155-57	67.1	3.0	—
					(159-60)[12]	(67.1	3.1)	
4f	H	3-ClC_6H_4	60	EtOH	130-32	67.2	3.0	—
					(134-35)[12]	(67.1	3.1)	
4g	H	4-ClC_6H_4	70	EtOH	202-03	67.2	3.1	—
					(204-05)[12]	(67.1	3.1)	
4h	H	3-BrC_6H_4	60	AcOH	142-44	59.7	2.8	—
					(146-47)[12]	(59.7	2.7)	
4i	H	4-BrC_6H_4	70	AcOH	218-20	59.8	2.7	—
					(216-18)[12]	(59.7	2.7)	
4j	H	2-$NO_2C_6H_4$	65	$CHCl_3$	172-74	65.3	2.9	—
					(173-74)[12]	(65.2	3.0)	
4k	H	3-$NO_2C_6H_4$	75	AcOH	178-79	65.3	3.0	—
					(180-81)[12]	(65.2	3.0)	
4l	H	4-$NO_2C_6H_4$	85	AcOH	198-99	65.3	3.0	—
					(196-97)[12]	(65.2	3.0)	
4m	H	4-$CH_3OC_6H_4$	65	EtOH	124-25	71.3	3.9	3.95 (*s*, 3H, $-OCH_3$),
					(126-27)[12]	(71.4	4.0)	7.30-8.30 (*m*, 1H, Ar-*H*)
4n	H	3,4-$O_2CH_2C_6H_3$	60	AcOH	165-67	68.7	3.2	5.95 (*s*, 2H, $-O_2CH_2$),
					(165)[12]	(68.7	3.3)	6.85-8.25 (*m*, 10H, Ar-*H*)
4o	H	C_4H_3O	55	$CHCl_3$	192-93	69.4	3.1	—
					(190-91)[12]	(69.3	3.2)	
4p	H	PhCH=CH	65	AcOH	190-92	75.7	4.3	—
					(191)[12]	(75.6	4.3)	
4q	H	3-$CHOC_6H_4$	55	AcOH	186-88	71.3	3.5	—
					(190)[12]	(71.2	3.4)	
4r	H	4-$CHOC_6H_4$	65	AcOH	202-04	71.3	3.5	—
					(204-05)[12]	(71.2	3.4)	
4s	—	—	55	AcOH	255-56	65.1	2.8	—
					(253-54)[12]	(65.2	2.8)	
4t	—	—	60	AcOH	286-88	65.2	2.9	—
					(285)[12]	(65.2	2.9)	—
4u	CH_3	CH_3	45	$CHCl_3$	88-90	70.2	4.3	2.05 *s*, 6H, $(CH_3)_2C=$
						(70.2	4.4)	7.25-8.35 (*m*, 6H, Ar-*H*)
4v	CH_3	C_6H_5	50	AcOH	130-32	74.1	4.2	2.30 (*s*, 3H, CH_3),
						(74.0	4.2)	7.30-8.30 (*m*, 11H, Ar-*H*)

*The IR spectra of **4** exhibited bands at 1590-1620 (C=C) and 960-980 cm^{-1} (out-off-plane deformation of C−H of exocyclic C=CH).

centrations of **2** (10, 100, 200, 500 and 1000 ppm). The bacterial population was found to decrease with increasing concentration. The bactericidal activity of **2** was optimum at 1000 ppm concentration.

Dimethyl 2,7-*dichloro*-9-*fluorenylphosphonate* (**1**)

A mixture of 9-bromo-2,7-dichlorofluorene (50 mmol) and trimethyl phosphite (50 mmol) was heated in an oil-bath under nitrogen atmosphere at 150° for 18 hr. Methyl bromide produced in the reaction was distilled off *in vacuo* and the residue extracted twice with ether. The ethereal layer on evaporation gave a pink compound which on recrystallization from *n*-hexane afforded pink crystal of **1**, yield 80%, m.p. 129-30° (Found: C, 52.5; H, 3.8%. $C_{15}H_{13}O_3PCl_2$ requires C, 52.5; H, 3.8%); IR(KBr); 1315 (P=O), 1035 cm^{-1} (P−O−C); PMR($CDCl_3$); 3.58 (*d*, 6H, $2\times OCH_3$), 4.60 (*d*, 1H, C_9-H, $J_{PH}=20$ Hz) and 7.28-8.40 (*m*, 6H, Ar−*H*).

Reaction of **2** *with aromatic aldehydes*:

General Procedure

To a stirred suspension of **2**, generated from **1** (5 mmol) and sodium hydride (5 mmol) in THF (50 ml), was added in an inert atmosphere (nitrogen) an appropriate aromatic aldehyde (5 mmol) and the mixture stirred at 100° for 4-10 hr, cooled to room temperature and excess of cold water added to it. The precipitated solid was extracted with ether. The ethereal layer was dried (anhyd. sodium sulphate) and solvent removed under reduced pressure to give a solid mass which on column chromatography afforded **4**. It was recrystallized from an appropriate solvent (Table 1).

Reaction of **2** *with isophthalaldehyde* (**3q**) *and terephthalaldehyde* (**3r**)

A mixture of **1** (8 mmol), sodium hydride (8 mmol) and **3q** or **3r** (4 mmol) in benzene (100 ml) was refluxed under nitrogen atmosphere for 10-14 hr. The precipitate containing sodium hydride and unreacted phosphonate was removed and the filtrate concentrated on a steam-bath under reduced pressure. The residue was chromatographed and the first fraction eluted with benzene-pet. ether (1:2) gave 9-(3-aldehydobenzylidene)-2,7-dichlorofluorene (**4q**) or 9-(4-aldehydobenzylidene)-2,7-dichlorofluorene(**4r**) in 20-30% yield. The second fraction eluted with benzene afforded 1,3-bis(2,7-dichloro-9-fluorenylidene)xylene(**4s**) or 1,4-bis(2,7-dichloro-9-fluorenylidene)xylene (**4t**) in 50% and 55% yields respectively.

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Studies in Nucleosides: Part XIV†—Synthesis of 2-Chloro/methoxy-6-N-substituted-9-(2-tetrahydrofuranyl)-9*H*-purines & Their Biological Activity‡

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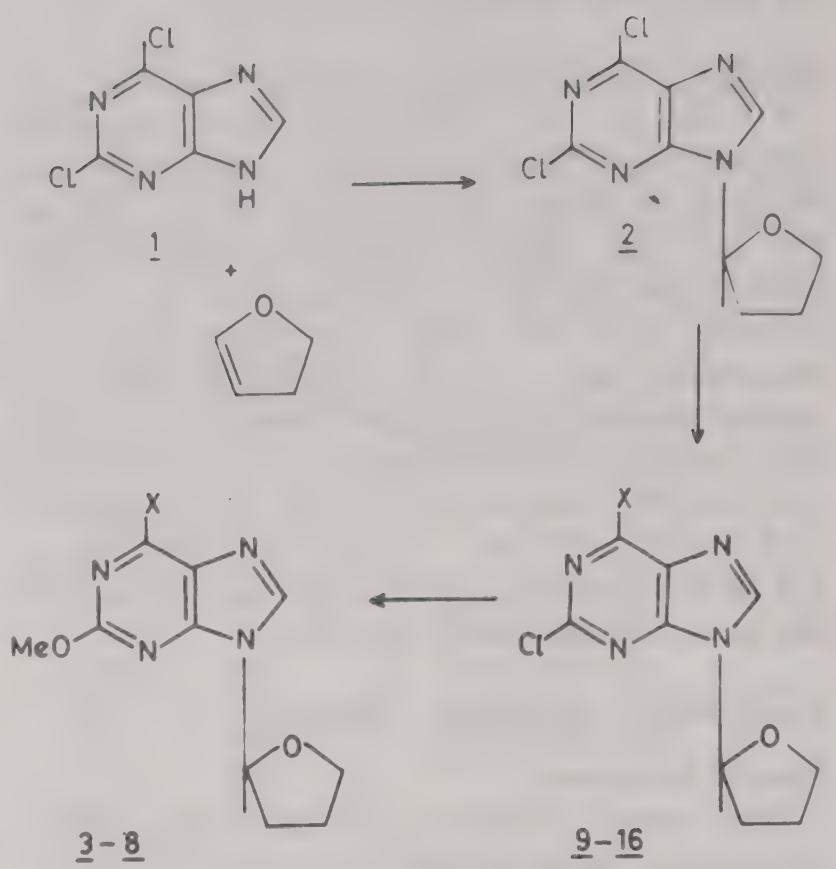
2-Methoxy-6-N-substituted-9-(2-tetrahydrofuranyl)-9*H*-purines (**3-8**) and 2-chloro-6-N-substituted-9-(2-tetrahydrofuranyl)-9*H*-purines (**9-16**) have been synthesised and screened against the semliki forest virus in Swiss albino mice. The compounds **3**, **11** and **13** in combination with an interferon inducer, mycoviral, exhibit 38, 30 and 63% enhancement of protection respectively against the virus. These compounds do not show any significant CVS activity.

Several 9-(2-tetrahydrofuranyl)-9*H*-purines are knwon to exhibit significant antitumour activity[2]. Recently 1-(2-tetrahydrofuranyl)-5-fluorouracil (Ftoraphur) has entered clinical trials as an anticancer agent[3]. Spongosine (2-methoxyadenosine), an abnormal purine nucleoside isolated from the sponge, *Cryptotethia crypta*, exhibits anticancer and vassodepressor activities[4]. These reports promted us to synthesize 2-methoxy-6-N-substituted-9-(2-tetrahydrofuranyl)-9*H*-purines. In the present note the synthesis, antiviral and CVS activities of 2-chloro-6-N-substituted-9-(2-tetrahydrofuranyl)-9*H*-purines (**9-16**) and 2-methoxy-6-N-substituted-9-(2-tetrahydrofuranyl)-9*H*-purines (**3-8**) are reported.

2,6-Dichloropurine (**1**), the key intermediate in the synthesis of 2,6,9-trisubstituted purines (**2-16**) was prepared by chlorination of 2,6-dithiopurine[5]. Condensation of **1** with 2,3-dihydrofuran in the presence of *p*-toluenesulphonic acid according to the Robins method[2], gave 2,6-dichloro-9-(tetrahydrofuranyl)-9*H*-purine (**2**) in 88% yield. Treatment of **2** with various amines in refluxing ethanol in the presence of dry potassium carbonate gave 6-alkylamino-2-chloro-9-(2-tetrahydrofuranyl)-9*H*-purines (**9-16**; Table 1). Refluxing **8-12** with sodium methoxide yielded the corresponding 6-alkylamino-2-methoxy-9-(2-tetrahydrofuranyl)-9*H*-purines (**3-8**; Table 1).



Antiviral activity

The antiviral activity of the synthesised compounds was determined against the semliki forest virus (SFV) *in vivo* according to the procedure described earlier[1]. The results are summarised in Table 1. Only compound **13** showed 63% protection against SFV in Swiss albino mice.

CVS activity

The compounds **3-16** were tested for their effect on blood pressure in anaesthetised cats following the procedure of Srimal *et al.*[8] through a pressure transducer, and generally found to lower blood pressure though not to any significant extent.

For general direction see earlier papers in the series[6,7], PMR, IR, UV and elemental analyses data of the compounds reported in Table 1 were in confirmity with the assigned structures.

6-*Alkylamino*-2-*methoxy*-9-(2-*tetrahydrofuranyl*)-9*H*-*purines* (**9-16**; *Table* 1)

A mixture of 2,6-dichloro-9-(2-tetrahydrofuranyl)-9*H*-purine (**2**; 1 mol), the appropriate amine (1 mol) and anhyd. K_2CO_3 (1 mol) was refluxed for 3 hr, filtered, solvent removed from the filtrate and the residue extracted with EtOAc. The extract was washed with dil. HCl, water, dried (Na_2SO_4), solvent removed, and the product crystallised from ethyl acetate-pet. ether and recrystallised from $CHCl_3$-pet. ether.

†For Part XIII of the series, see ref. 1.
‡CDRI communication no. 3783.

Table 1—Characterization and Antiviral Activity Data of 2-Chloro/methoxy-6-N-substituted-9-(2-tetrahydrofuranyl)-9*H*-purines (**3-16**)

Compd	X*	Mol. formula	m.p. °C	Yield (%)	Antiviral activity (%survival)
3	*p*-Tolylethylamino	$C_{19}H_{23}N_5O_2$	165-68	25	38
4	NH_2	$C_{10}H_{13}N_5O_2$	195-98	53	13
5	Piperidino	$C_{15}H_{21}N_5O_2$	70-71	31	20
6	Morpholino	$C_{14}H_{19}N_5O_3$	63-65	36	20
7	N^4-Methylpiperazin-1-yl	$C_{15}H_{22}N_6O_2$	Oil	51	13
8	N^4-Phenylpiperazin-1-yl	$C_{20}H_{24}N_6O_2$	235	59	15
9	Isopropylamino	$C_{12}H_{16}ClN_5O$	Oil	23	—
10	Diethylamino	$C_{13}H_{18}ClN_5O$	Oil	40	—
11	*p*-Tolylethylamino	$C_{18}H_{20}ClN_5O$	148	82	30
12	NH_2	$C_9H_{10}ClN_5O$	300	54	13
13	Piperidino	$C_{14}H_{18}ClN_5O$	85	20	63
14	Morpholino	$C_{13}H_{16}ClN_5O$	Oil	35	20
15	N^4-Methylpiperazin-1-yl	$C_{14}H_{19}ClN_6O$	80	36	13
16	N^4-Phenylpiperazin-1-yl	$C_{19}H_{21}ClN_6O$	170	47	10

*The amines used in the preparation of **3-16** are represented by XH.

6-*Alkalamino*-2-*methoxy*-9-(2-*tetrahydrofuranyl*)-9*H*-*purines* (**3-8**; *Table* 1)

A solution of 2-chloro derivatives (**11-16**; 1 mol) in dry methanol was refluxed with NaOMe for 1 hr under nitrogen atmosphere. The resulting mixture was rendered acidic with AcOH and the product extracted with EtOAc. The extract was washed with water, dried (Na_2SO_4), solvent removed, and the product crystallised from EtOAc-pet. ether.

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Isoquinolylquinoline Derivatives: Part IV[a]—Synthesis of Some 4-Substituted 3-(3′,4′-Dihydro-3′-methyl-1′-isoquinolyl)-7-chloroquinoline Derivatives as Possible Trypanocidal Agents[b]

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Cyclisation of the amide Ib using PPA and $POCl_3$ affords the corresponding 3-methyl-3,4-dihydroisoquinolylquinoline derivative (IIIa) which on treatment with $POCl_3$ is converted into IIIb. This compound (IIIb) reacts with ammonia (gas), hydrazine hydrate, morpholine, piperidine and pyrrolidine to give the 4-substituted-amino derivatives IIIc-g respectively. But with $NaOC_2H_5$, IIIb affords two distinctly different aromatic compounds Vb and Vc. Reduction of IIIa with $NaBH_4$ gives the desired compound IV, whereas dehydrogenation of IIIb with sulphur in the presence of tetralin leads to the formation of a new product VI. Compound IIIb also reacts with 4-acetamido-α-(diethylamino/N-morpholino/N-piperidino)-*o*-cresols to furnish three azaheterocyclic derivatives (VIIIa-c) which are structurally analogous to the noted antimalarial amodiaquine.

It has been reported in our earlier paper[1] that some isoquinolylquinoline compounds having structural analogy with the established quinoline antimalarial amodiaquine possess significant antifilarial activity. Considering that certain antifilarial agents containing either quinoline or isoquinoline nucleus in their molecular framework are found to exert trypanocidal activity[2-6], it was thought worthwhile to extend our earlier work. The synthesis of the compounds with general structures III and VIII and evaluation of their trypanocidal activity are reported here.

The starting intermediate Ib, prepared by heating ethyl 7-chloro-4-hydroxyquinoline-3-carboxylate[7] (Ia) with α-methyl-β-phenethylamine[8] (IIa) was cyclised in the presence of PPA and $POCl_3$ according to the condition of Bischler-Napieralski reaction[9] to afford IIIa in 42% yield. Compound IIIa on dehydrogenation either with sulphur in the absence of a solvent or with Pd/C in tetralin did not afford Va. It has been reported from this laboratory[10,11] that cyclisation of the amide of type **A** with P_2O_5/xylene affords the corresponding completely aromatised product of the type **B**. With this approach the intermediate amide Ic, prepared by reacting the quinoline ester (Ia) with α-methyl-α-carbethoxy-β-phenethylamine[12] (IIb), was subjected to cyclodehydration with P_2O_5/xylene or PPA or PPA and $POCl_3$ mixture but in no case the desired product Va could be obtained. The compound IIIa, however, on reduction with $NaBH_4$ in ethanolic medium yielded the expected product IV. Reaction of IIIa with $POCl_3$ furnished IIIb.

The amides Ib and Ic showed sharp similarity in their UV spectrum. In the case of IIIa and IV the twin peaks (between 240 and 330 nm) may be attributed to the presence of Bz-chloro-4-quinolone function as explained by Steck *et al.*[13]. The single UV absorption maximum at 235 nm of IIIb is characteristic of isoquinolylquinoline system having 4-chloro substitution with respect to quinoline ring[14,15].

The compound IIIb reacted with ammonia (gas) in the presence of phenol at elevated temperature to afford the 4-aminoquinoline derivative IIIc, and on heating with hydrazine hydrate in dioxan medium, gave the highly basic compound IIId. With secondary amines such as morpholine, piperidine and pyrrolidine, IIIb reacted to afford the corresponding azaheterocyclic derivatives (IIIe, IIIf and IIIg).

Very interestingly it was observed that when IIIb was heated with $NaOC_2H_5$ solution, the corresponding 4-ethoxyquinoline derivative (IIIh) was not formed. Instead, two distinctly different aromatic compounds Vb and Vc were isolated from the reaction mixture, Vc being more polar than Vb. For authentic synthesis of compound Vb, subsequent attempt to dehydrogenate IIIb, by heating with sulphur alone, was unsuccessful.

Compound IIIb on heating with sulphur in tetralin, however, led to the formation of an entirely new compound VI, the mass spectrum of which exhibited molecular ion peak at *m/z* 465 besides the only

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[a]Presented in part at (i) the Annual Session of the Indian Science Congress and Indian Pharmaceutical Congress: Chakravorti S S & Das M, *Proc 53rd Indian Sci Congr Abstr Part III Sec Chem*, (1976) 66, *Proc 64th Indian Sci Congr Abstr Part III Sec Chem*, (1977) 27, *Proc 65th Indian Sci Congr Abstr Part III Sec Chem*, (1978) 54, *Proc XIX Indian Pharm Congr Abstr*, **A18** (1977) 4; (ii) the Golden Jubilee Symposium, Institution of Chemists (India): Chaudhuri S, Das M & Chakravorti S S, *Proc of Institution of Chemists (India) Part IV*, **50** (1978) 99.

[b]Part of Ph.D. Thesis of Michael Das submitted to the University of Calcutta, 1979.

[c]Present address: Department of Chemistry, Darjeeling Govt College, Darjeeling 734101, West Bengal.

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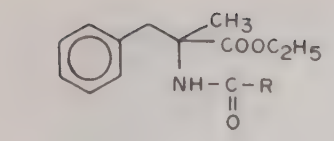
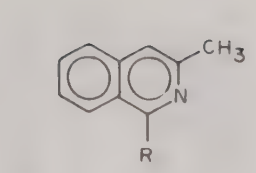


A



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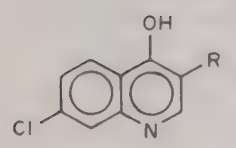
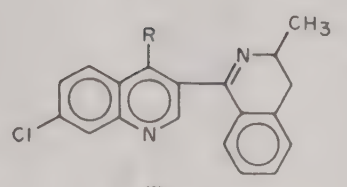


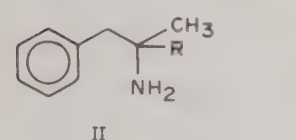
I

a) R = $COOC_2H_5$
b) R = $CONH \cdot CH(CH_3) - CH_2 \cdot C_6H_5$
c) R = $CONH \cdot C(CH_3)(CH_2 \cdot C_6H_5)(COOC_2H_5)$



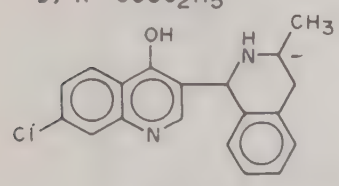
III

a) R = OH
b) R = Cl
c) R = NH_2
d) R = $NH \cdot NH_2$
e) R = morpholino
f) R = piperidino
g) R = pyrrolidino
h) R = OC_2H_5

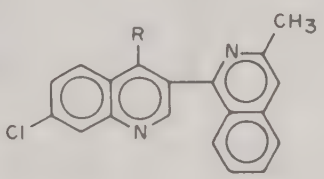


II

a) R = H
b) R = $COOC_2H_5$

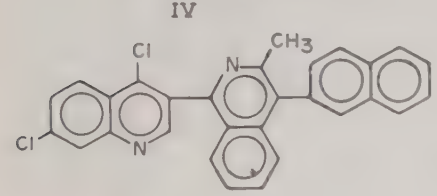


IV

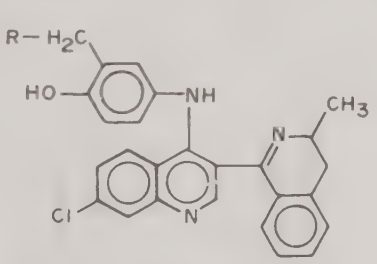


V

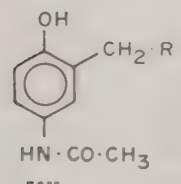
a) R = OH
b) R = $OCH_2 \cdot CH_3$
c) R = Cl



VI



VIII



VII

a) R = $-N(C_2H_5)(C_2H_5)$
b) R = morpholino
c) R = piperidino

a) R = $-N(C_2H_5)(C_2H_5)$
b) R = morpholino
c) R = piperidino

significant peak at m/z 336 corresponding to the loss of naphthalene molecule from M^+. From this observation it is evident that during the above reaction, both the 3,4-dihydroisoquinoline part of IIIb and tetralin were dehydrogenated simultaneously with the generation of a new C−C bond. Since tetralin is the solvent of dehydrogenation, it is quite logical to expect that tetralin initially underwent nucleophilic addition at its unhindered β-position[16], similar to that of Friedel-Craft reaction with the intermediate cation generated from IIIb ultimately yielding the β-naphthalene substituted product VI. It is well known that in any substitution reaction with tetralin, attack at its β-position is favoured over that at α-position. The 200 MHz PMR spectral data of VI (Table 1), with the absence of any singlet around δ8.0, further substantiate that C-4 of isoquinoline ring is involved in the C−C linkage with naphthalene ring in its β-position.

Compound IIIb was further reacted with 4-acetamido-α-diethylamino-*o*-cresol[17] (VIIa), 4-acetamido-α-N-morpholino-*o*-cresol[17] (VIIb) and 4-acetamido-α-N-piperidino-*o*-cresol (VIIc) in HCl medium according to the method of Burckhalter *et al.*[17] to afford the three isoquinolylquinoline derivatives VIIIa, VIIIb and VIIIc respectively which have some structural analogy with the noted antimalarial amodiaquine. The mass spectra of these three compounds showed the presence of common ion peaks at m/z 410, 412, 425, 426, 427 and 428 out of which the relative intensity of the ions m/z 412 and 427 were greater in comparison to the others. In each case, the molecular ion (M^+) underwent benzylic cleavage with hydrogen transfer from diethylamino, morpholino or piperidino residue producing the ion peak at m/z 427 which by the loss of a hydrogen radical produced the ion m/z 426. The peak at m/z 426 may also be plausible due to benzylic cleavage of the parent molecular ion (M^+) (Chart 1). From the study of the relative intensity of the fragments m/z 426 and 427 of the three compounds VIIIa-c, it has been found that benzylic cleavage is more prominent in compound VIIIb than in VIIIa and VIIIc.

From preliminary pharmacological screening data of the compounds IIIa, IIIb, IIId and VIIIa-c it appears that none of them possesses any significant trypanocidal activity against *T. cruzi* and *T. evansi* in mice.

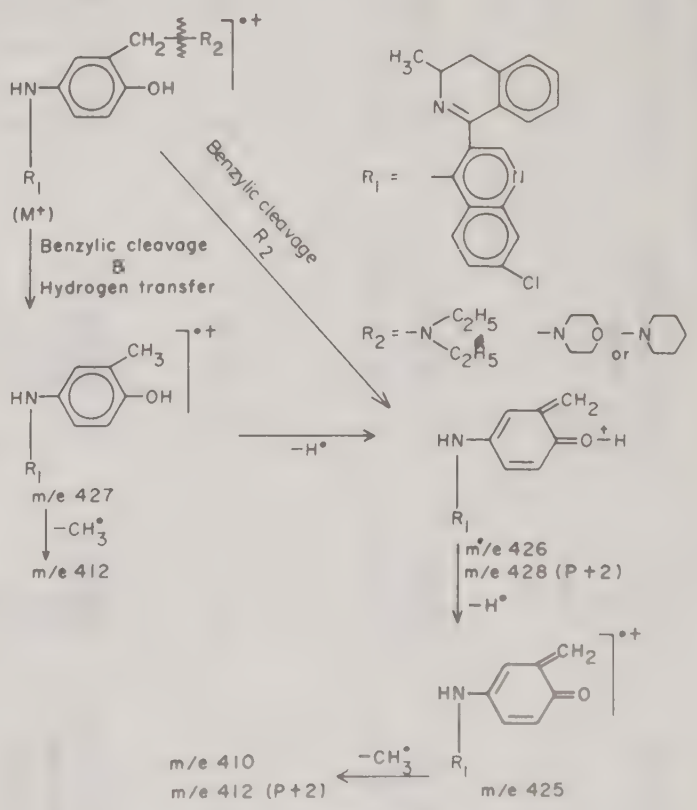


Chart 1

Table 1—Characterisation Data of Compounds (I-VIIIa-c) and Their Derivatives

Compd	m.p. °C	Yield (%)	Crystallised from*	Colour†	Mol. formula	N(%)‡ Found	N(%)‡ (Calc)	UV (EtOH) nm(log ε)		PMR (Solvent) δ, ppm
Ib	138-40	52	EtOH	C	$C_{19}H_{17}N_2O_2Cl$	8.1	8.2	260 (4.41) 315 (4.01)	(CF_3COOH)	:1.42 (*d*, *J*=7 Hz, 3H, CH_3), 2.99 (*d*, *J*=7 Hz, 2H, CH_2), 4.33-4.83 (*m*, br, 1H, >CH), 7.25 (*s*, 5H, Ar-*H*), 7.66-8.40 (*m*, 3H, Ar-*H*), 8.63 (*s*, 1H, C_2-H), 9.37 (*s*, 1H, OH)
Ic	203-4	5	EtOH	C	$C_{22}H_{21}N_2O_4Cl$	6.7	6.8	260 (4.38) 315 (4.04)	($CDCl_3$ + CD_3COCD_3)	:1.33 (*t*, *J*=7 Hz, 3H, ester CH_3), 1.75 (*s*, 3H, CH_3), 3.46 (*s*, 2H, C_6H_5-CH_2), 4.30 (*q*, *J*=6 Hz, 2H, ester OCH_2), 7.25 (*s*, 5H, Ar-*H*), 7.30-8.30 (*m*, 3H, Ar-*H*), 8.40 (*s*, 1H, C_2-H), 10.73 (*s*, 1H, NH), 11.50 (br, 1H, OH)
IIIa	218	42	EtOH	Y	$C_{19}H_{15}N_2OCl$	8.8	8.7	245 (4.22) 280 (4.31) 360 (3.92) 395 (4.06)	(CF_3COOH)	:1.63 (*d*, *J*=7 Hz, 3H, CH_3), 3.18 (*t*, 2H, CH_2), 4.00-4.50 (complex *m*, 1H, −C−H), 7.33-8.40 (*m*, 7H, Ar-*H*), 8.83 (*s*, 1H, C_2-H), 9.87 (*br*, 1H, OH)
IIIa. Picrate	265(d)	—	EtOH	Y	$C_{19}H_{15}N_2OCl.C_6H_3N_3O_7$	12.6	12.7			
IIIa. HCl	215	—	H_2O	C	$C_{19}H_{15}N_2OCl.HCl$	7.7	7.8			
IIIa.CH_3I	260	—	EtOH	Y	$C_{19}H_{15}N_2OCl.CH_3I$	6.1	6.0			
IIIb	170	63	EtOH	C	$C_{19}H_{14}N_2Cl_2$	8.3	8.2	235 (4.77)	($CDCl_3$)	:1.58 (*d*, *J*=7 Hz, 3H, CH_3), 2.92 (*d*, 2H, CH_2), 3.58-4.25 (br *m*, 1H, C_3-H), 6.83-8.20 (complex *m*, 7H, Ar-*H*), 8.33 (*s*, 1H, C_2-H)
IIIb. Picrate	185	—	EtOH	Y	$C_{19}H_{14}N_2Cl_2.C_6H_3N_3O_7$	12.4	12.3			
IIIb. CH_3I	220(d)	—	EtOH	Y	$C_{19}H_{14}N_2Cl_2.CH_3I$	5.7	5.8			
IIIc	242-43	74	EtOH	Y	$C_{19}H_{16}N_3Cl$	12.9	13.1	255 (4.63) 280 (4.28)	(DMSO-d_6)	:1.43 (*d*, *J*=7.5 Hz, 3H, CH_3), 2.83 (*d*, 2H, CH_2), 3.40 (*s*, 2H, NH_2), 3.46-3.83 (br *m*, 1H, C_3-H), 7.25-8.30 (*m*, 7H, Ar-*H*), 8.43 (*s*, 1H, C_2-H)
IIIc. Picrate	>300	—	EtOH	Y	$C_{19}H_{16}N_3Cl.2C_6H_3N_3O_7$	16.0	16.2			
IIIc.HCl	305(d)	—	EtOH-Et_2O	C	$C_{19}H_{16}N_3Cl.2HCl$	10.5	10.6			
IIId	246-47	45	EtOH (aq.)	C	$C_{19}H_{17}N_4Cl$	16.7	16.6	245 (4.55) 295 (3.90)	(CF_3COOH)	:1.63 (*d*, 3H, CH_3), 3.23 (*d*, 2H, CH_2), 4.07 (br *m*, 1H, C_3-H), 7.10 (*br*, 2H, NH_2), 7.70-8.73 (*m*, 7H, Ar-*H*), 8.90 (*s*, 1H, C_2-H), 9.56 (*s*, 1H, NH)
IIId. Picrate	276-77(d)	—	EtOH	Y	$C_{19}H_{17}N_4Cl.2C_6H_3N_3O_7$	17.7	17.6			
IIId. HCl	295-96(d)	—	EtOH (anhyd)	LY	$C_{19}H_{17}N_4Cl.2HCl$	13.8	13.7			
IIIe**	132-33	39	Pet. ether	C	$C_{23}H_{22}N_3OCl$	10.9	10.7	235 (3.71) 260 (3.41)	(CCl_4)	:1.45 (*d*, *J*=6 Hz, 3H, CH_3), 2.50-2.83 (*t*, 2H, C_4-CH_2), 3.05 [br *s*, 4H, $-CH_2-N-CH_2-$], 3.63 (br *s*, 4H, $-CH_2-O-CH_2$), 3.63-4.20 (*br*, 1H, C_3-H), 6.67-8.10 (complex *m*, 7H, Ar-*H*), 8.47 (*s*, 1H, C_2-H)

Contd

Table 1—Characterisation Data of Compounds (I-VIIIa-c) and Their Derivatives—*Contd*

Compd	m.p. °C	Yield (%)	Crystallised from*	Colour†	Mol. formula	N(%)‡ Found	N(%)‡ (Calc)	UV (EtOH) nm (log ε)		PMR (Solvent) δ, ppm
IIIe. Picrate	267-68(d)	—	EtOH	Y	$C_{23}H_{22}N_3OCl.C_6H_3N_3O_7$	13.4	13.5			
IIIf	83-5	42	Pet. ether	C	$C_{24}H_{24}N_3Cl$	10.7	10.8			
IIIf. Picrate	252-53(d)	—	EtOH	Y	$C_{24}H_{24}N_3Cl.2C_6H_3N_3O_7$	14.7	14.8			
IIIg. Picrate	267-68	—	EtOH	Y	$C_{23}H_{22}N_3Cl.2C_6H_3N_3O_7$	15.0	15.1			
IV	185	67	EtOH-H_2O(1:1)	C	$C_{19}H_{17}N_2OCl$	8.5	8.6	255 (4.58) 290 (3.71) 325 (4.05)	(CF_3COOH)	:1.75 (*d*, $J=7$ Hz, 3H, CH_3), 3.33 (*d*, $J=7$ Hz, 2H, CH_2), 3.66-4.33 (*br*, 1H, $C_{3'}$-H), 6.17 (br *s*, 1H, NH), 6.83 (br *d*, 1H, $C_{1'}$-H), 6.97-8.33 (*m*, 7H, Ar-*H*), 8.50 (*s*, 1H, C_2-H), 8.73 (br *s*, 1H, OH)
IV. Picrate	260(d)	—	EtOH	Y	$C_{19}H_{17}N_2OCl.C_6H_3N_3O_7$	12.7	12.6			
Vb	146-47	18	$CHCl_3$-Pet. ether	C	$C_{21}H_{17}N_2OCl$	8.1	8.0		(CF_3COOH)	:0.66-0.75 (*t*, 3H, $-OCH_2CH_3$), 2.33 (*s*, 3H, $C_{3'}$-CH_3), 3.00-3.66 (*m*, 2H, $-OCH_2CH_3$), 7.20-8.10 (*m*, 8H, Ar-*H*), 8.50 (*s*, 1H, C_2-H)
Vc	176	1	—	C	$C_{19}H_{12}N_2Cl_2$	8.5	8.3			
VI[δ]	163-64	13	$CHCl_3$-Pet. ether	LY	$C_{29}H_{18}N_2Cl_2$	6.2	6.0	219 (4.92) 236 (4.79) 280 (4.26) 329 (4.10)	($CDCl_3$)	:2.36 (*s*, 3H, $C_{3''}$-CH_3), 6.90 (*d*, 1H, $C_{3''}$-H), 7.14 (br *s*, 1H, $C_{1''}$-H), 7.23 (*d*, 1H, $C_{4''}$-H), 7.26-7.46 [*m*, 4H ($C_{6'}$-, $C_{7'}$-, $C_{6''}$- and $C_{7''}$-H], 7.46-7.65 [*m*, 5H ($C_{6'}$-, $C_{5'}$-, $C_{7'}$-, $C_{5''}$-, and $C_{8''}$-H], 8.24 (br *s*, 1H, C_8-H), 8.52 (*d*, 1H, C_5-*H*), 8.92 (*s*, 1H, C_2-H)
VIIc	161-62	80	EtOH-H_2O (5:2)	C	$C_{14}H_{20}N_2O_2$	11.2	11.3			
VIIIa	138-39	20	Pet. ether	Y	$C_{30}H_{31}N_4OCl$	11.2	11.2	220 (4.59) 350 (3.88)	(CCl_4)	:1.10 [*t*, $J=7$ Hz, 6H, $-N(CH_2CH_3)_2$, 1.42 (*d*, $J=7$ Hz, 3H, $C_{3'}$-CH_3), 2.53 [*q* overlapping, $J=7$ Hz, 6H, $-N(CH_2CH_3)_2$ and $C_{4'}$-CH_2], 3.56 (*s* alongwith br *m*, 3H, CH_2 *ortho* to phenolic OH and $C_{3'}$-H), 6.50-7.90 (complex *m*, 10H, Ar-*H*), 8.63 (*s*, 1H, C_2-H), 11.03 (br *s*, 1H exchangeable with D_2O, phenolic OH)
VIIIa. HCl	240-41(d)	—	EtOH-Et_2O	OR	$C_{30}H_{31}N_4OCl.2HCl$	9.7	9.8			
VIIIb	128-30	20	Pet. ether	Y	$C_{30}H_{29}N_4O_2Cl$	11.0	10.9	220 (4.50) 350 (3.81)	(CCl_4)	:1.46 (*d*, $J=7$ Hz, 3H, $C_{3'}$-CH_3), 2.30-2.76 (*m*, 6H, $-CH_2-N-CH_2-$ and benzylic CH_2), 3.33-4.00 (complex *m*, 7H, CH_2 *ortho* to phenolic OH overlapped with highly coupled $C_{3'}$-H) and $-CH_2-O-CH_2$), 6.40-8.00 (*m*, 10H, Ar-*H*), 8.70 (*s*, 1H, C_2-H), 11.00 (*s*, 1H, exchangeable with D_2O, phenolic OH)

Contd

Table 1—Characterisation Data of Compounds (I-VIIIa-c) and Their Derivatives—*Contd*

Compd	m.p. °C	Yield (%)	Crystallised from*	Colour†	Mol. formula	N(%)‡ Found	N(%)‡ (Calc)	UV (EtOH) nm(log ε)	PMR (Solvent) δ, ppm
VIIIc	102-3	2	Pet. ether	Y	$C_{31}H_{31}N_4OCl$	10.9	11.0	220 (4.71) (CDCl$_3$) 350 (4.01)	:1.44 (*d*, *J* = 7 Hz, 3H, C_3-CH_3), 1.56 (br *s*, 6H, $-CH_2-CH_2-CH_2$ of piperidine nucleus), 2.48 (br *s*, 4H, $-CH_2-N-CH_2$ –), 2.70 (*d*, 2H, benzylic CH_2), 3.52 (*s*, 2H, CH_2 *ortho* to phenolic OH), 3.80 (*t*, 1H, C_3-H), 6.36 (*br*, 1H exchangeable with D_2O, NH), 8.74 (*s*, 1H, C_2-H), 10.38 (*s*, 1H exchangeable with D_2O, OH)

*Pet. ether (b.p. 60-80°)
†C = Colourless; Y = Yellow; LY = Light yellow; OR = Orange red.
‡Satisfactory C, H analyses for all the compounds and Cl analyses for the hydrochlorides were obtained.
**UV (0.1 *N* HCl): 225, 245, 265, 310, 400 nm (log ε 4.52, 4.26, 4.24, 4.27, 3.86).
$^{\delta}$UV (0.1 *N* HCl): 216, 324 (log ε 4.98, 4.42).

Melting points were recorded on a Buchi melting point apparatus and are uncorrected. UV spectra were taken on a Hilger spectrophotometer model H700 using quartz cells, IR spectra on a Beckman IR-8 spectrophotometer (ν_{max} in cm^{-1}) and 60 MHz PMR spectra (chemical shifts in, δppm) on a varian A-60 instrument using TMS as internal standard.

N-(α-Methyl-β-phenethyl)-7-chloro-4-hydroxyquinoline-3-carboxamide (*Ib*)

Ethyl 7-chloro-4-hydroxyquinoline-3-carboxylate[7] (Ia, 25 g) and α-methyl-β-phenethylamine[8] (IIa, 14 g) were mixed thoroughly and the mixture was heated in an oil-bath at 180-90° for 6 hr under suction. The molten mass on cooling and trituration with ether furnished a solid product which after crystallisation afforded Ib as microcrystals.

N-(α-Methyl-α-carbethoxy-β-phenethyl)-7-chloro-4-hydroxyquinoline-3-carboxamide (*Ic*)

A mixture of Ia (25 g) and α-methyl-α-carbethoxy-β-phenethylamine[12] (IIb, 25 g) was heated at 170° for 6 hr under suction, cooled, and triturated with ether. The ethereal extract after concentration afforded Ic on crystallisation.

4-Hydroxy-3-(3′,4′-dihydro-3′-methyl-1′-isoquinolyl)-7-chloroquinoline (*IIIa*)

In a flask, protected from moisture, P_2O_5 (75 g) was treated with orthophosphoric acid (85%, 50 ml) and the mixture heated in an oil-bath at 95-100° for 2 hr under stirring. To the cooled syrupy mass were added carboxamide (Ib, 10 g) and $POCl_3$ (30 ml) gradually under stirring (oil-bath temp 80°). The temperature was then slowly raised to 135-40° avoiding frothing and kept at this temperature for 10 hr. After cooling, the mixture was treated with ice-water and filtered (charcoal). The filtrate on basification with ammonium hydroxide afforded a yellow solid product which crystallised to furnish the free base (IIIa).

3-(3′,4′-Dihydro-3′-methyl-1′-isoquinolyl)-4,7-dichloroquinoline (*IIIb*)

To the compound IIIa (3 g) was slowly added freshly distilled $POCl_3$ (30 ml) during 30 min under stirring and the resultant solution heated under reflux in an oil-bath at 120° for 2 hr and about half the quantity of $POCl_3$ distilled under reduced pressure. The residual liquid, on cooling, was poured into ice and water, treated with charcoal and filtered. The filtrate was basified slowly with ammonium hydroxide in the cold to furnish a cream coloured solid which was filtered, dried and crystallised to furnish IIIb.

4-Amino-3-(3′,4′-dihydro-3′-methyl-1′-isoquinolyl)-7-chloroquinoline (*IIIc*)

A mixture of the compound IIIb (5 g) and freshly distilled phenol (20 g) was heated in an oil-bath at 100-10° for 1 hr. To the clear solution, thus obtained, dry ammonia gas was passed for 2.5 hr at 150-60°. The reaction mixture was cooled and triturated with NaOH solution (10%, 300 ml) to furnish a light yellow solid which crystallised to afford IIIc.

4-Hydrazino-3-(3′,4′-dihydro-3′-methyl-1′-isoquinolyl)-7-chloroquinoline (*IIId*)

The chloro compound IIIb (3 g) was taken in dioxan (50 ml) to which hydrazine hydrate (80%, 3 g) was added and the mixture heated under reflux at 110-20° for 2 hr. The solvent was removed by distillation under reduced pressure and the residual mass triturated with water to afford a solid product which crystallised to furnish IIId.

4-(Morpholino)-3-(3′,4′-dihydro-3′-methyl-1′-isoquinolyl)-7-chloroquinoline (*IIIe*)

A mixture of IIIb (3 g) and morpholine (1 g) was heated at 130-40° for 4 hr, cooled and triturated with anhyd. acetone (25 ml). The solid (morpholine hydrochloride) that separated out was filtered and washed with acetone. The filtrate on concentration furnished a semisolid mass which after purification by acid-base treatment and final crystallisation afforded IIIe.

4-(Piperidino)-3(3′,4′-dihydro-3′-methyl-1′-isoquinolyl)-7-chloroquinoline (*IIIf*)

The compound IIIb (3 g) was mixed with piperidine (1 g) and heated at 130-40° for 4 hr. After cooling, the mixture was worked up as in the case of IIIe. The light yellow solid thus isolated was finally crystallised to afford IIIf which absorbed moisture and became coloured on standing.

4-(Pyrrolidino)-3-(3′,4′-dihydro-3′-methyl-1′-isoquinolyl)-7-chloroquinoline (*IIIg*)

A mixture of IIIb (3 g) and pyrrolidine (1 g) was heated on a boiling water-bath for 4 hr. The resultant thick liquid was washed with water and extracted with ether. The ethereal layer was dried with anhyd. Na_2SO_4 and concentrated to afford IIIg as a thick brown thermolabile liquid which could not be distilled even under high vacuum and was characterised as dipicrate.

4-Hydroxy-3-(1′,2′,3′,4′-tetrahydro-3′-methyl-1′-isoquinolyl)-7-chloroquinoline (*IV*)

To a solution of IIIa (1.5 g) in anhyd. ethanol (100 ml) was added $NaBH_4$ (0.5 g) gradually under shaking. The resulting mixture was kept at room temperature for 30 min, then heated under reflux on water-bath for 3 hr, and filtered. The filtrate on concentration under reduced pressure furnished a solid product which crystallised to afford IV.

4-Ethoxy-3-(3′-methyl-1′-isoquinolyl)-7-chloroquinoline (*Vb*) *and 3-(3′-methyl-1′-isoquinolyl)-4,7-dichloroquinoline* (*Vc*)

A mixture of IIIb (1 g) and 10% $NaOC_2H_5$ solution in ethanol (10 ml) was heated under reflux in water-bath for 3 hr, cooled, and filtered. The filtrate after concentration, was diluted with water to afford a solid which was filtered and subsequently purified through column chromatography over basic Al_2O_3 using 20% $CHCl_3$-80% pet ether as eluent. The eluate on crystallization gave Vb (0.2 g); MS: *m/z* 348 (M^+), 333 ($M^+ - CH_3$), 319 ($M^+ - CH_2.CH_3$), 303 ($M^+ - OCH_2.CH_3$).

The basic aq. filtrate after separation of compound Vb was extracted with benzene, and the benzene layer dried over anhyd. Na_2SO_4 and concentrated to give a yellow solid which on column chromatography over basic Al_2O_3 afforded two different products: (i) a colourless fluffy solid (10 mg), obtained by elution with 5-10% $CHCl_3$ in pet. ether, was characterised as Vc, m.p. 176°; MS: *m/z* 339 (M^+); PMR ($CDCl_3$): 2.76 (*s*, $3H, CH_3$), 7.40-4.48 (*m*, 8H, Ar-*H*), 9.24 (*s*, 1H, C_2-H), and (ii) a yellowish crystalline solid (m.p. 218°), obtained by elution with 50% $CHCl_3$ in pet. ether, was identified as IIIa by direct comparison (m.m.p., co-TLC, IR and PMR spectra) with an authentic sample.

3-[3′-Methyl-4′-(β-naphthyl)-1′-isoquinolyl]-4,7-dichloroquinoline (*VI*)

To a solution of IIIb (1 g) in tetralin (15 ml) was added sulphur powder (1 g), and the mixture heated at 200-10° in an oil-bath for 3 hr till the evolution by H_2S ceased. After cooling, the tetralin layer was repeatedly extracted with 50% HCl. The acid layer on neutralization with $NaHCO_3$ furnished a yellowish solid (TLC single spot) which after purification by column chromatography over basic Al_2O_3 using 20% $CHCl_3$ in pet. ether as eluant and subsequent crystallisation afforded the compound VI.

4-Acetamido-α-(N-piperidino)-o-cresol (*VIIc*)

A mixture of *p*-acetamidophenol (15.1 g, 0.1 mole), piperidine (8.5 g, 0.1 mole), formaldehyde (40%, 8 ml) and ethanol (25 ml) was heated under reflux on a boiling water-bath for 4 hr. Removal of solvent gave a semisolid mass which after trituration with water and crystallisation furnished VIIc; PMR ($CDCl_3$): 1.50 (br *s*, 6H, $3 \times CH_2$ of piperidine ring), 2.03 (*s*, 3H, acetylamino CH_3), 2.40 (br *s*, 4H, $-H_2C-H-CH_2$

−), 3.53 (*s*, 2H, $-CH_2-N<$), 6.63-7.30 (*m*, 3H, Ar-*H*), 8.35 (*s*, 1H, NH) and 11.21 (*s*, 1H, OH) (both confirmed by D_2O exchange).

General procedure for the preparation of 4-[3″-(*diethylaminomethyl/N-morpholinomethyl/N-piperidinomethyl*)-4″-*hydroxyanilino*]-3-(3′,4′-*dihydro*-3′-*methyl*-1′-*isoquinolyl*)-7-*chloroquinolines* (*VIIIa-c*)

4-Acetamido-α-(diethylamino/N-morpholino/N-piperidino)-*o*-cresol (VIIa-c each, 0.01 mol) were separately hydrolysed with conc. HCl (6 ml) by heating under reflux for 1 hr. The acidic solution in each case was brought to *p*H 4 after cooling and the compound IIIb (3 g, 0.01 mol) added to it. The reaction mixture was heated on a steam-bath for 8-10 hr in the case of both VIIa and VIIb and 20 hr in the case of VIIc. It was then diluted with boiling water, treated with charcoal, filtered and the filtrate basified with dil. NH_4OH to afford VIII which crystallised from an appropriate solvent.

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Synthesis, Reactions & Biological Activity of 3-[*p*-(N-Methyl/ethyl-N-phenylcarbamoyl)]phenylsydnones

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The title sydnones (I) have been prepared from *p*-aminobenzanilides and converted into pyrazolyl derivatives (II,III). These compounds exhibit antibacterial activity comparable to that of standard compounds (sulphanilamide and phenol) at different concentrations.

In our search for medicinally important sydnone derivatives we have prepared the title compounds (I) from the easily available and biologically active[1] *p*-amino-N-methyl/ethyl-benzanilides[2,3] following the standard procedure[4] and converted the sydnones into pyrazoles (II and III) by reaction with DMAD and DBA. Both the sydnones (I) and pyrazoles (II,III) were characterised by elemental analyses and spectral data. Their IR spectra exhibited an amide C=O band at 1650 cm^{-1}. In addition to this, the sydnones (I) showed IR bands at 1750 (sydnones C=O) and 3160-3200 cm^{-1} (sydnone C–H).

The PMR ($CDCl_3$) spectrum of Ia displayed a singlet at δ 3.7 (CH_3), another singlet at 7.0 (sydnone C–H) and a multiplet centered at 7.6 (phenyl protons), and that of Ib exhibited at triplet centered at 1.2 (CH_3), a quartet centered at 3.9 (CH_2), a singlet at 6.8 (sydnone C–H) and a multiplet centered at 7.3 (phenyl protons).

Biological activity

The sydnones and their corresponding pyrazoles (I-III) were subjected to antibacterial screening against *S. aureus*, *E. coli*, *P. vulgaris* and *Pseudomonas pyocynea* employing the cup-plate method[5]. Sulphanilamide and phenol were used as standards. Zone of inhibition was measured after 24 hr. The test compound (10 mg) was dissolved in 10 ml of distilled DMF to give the drug solution from which solutions of different concentrations, i.e. 100 μg/0.1 ml, 50 μg/0.1 ml and 25 μg/0.1 ml, were made and 0.1 ml of the solution was used for screening. All the six compounds tested exhibited activity comparable to that of the standard compounds (Table 1).

Melting points were determined in open capillary tubes and are uncorrected. IR (KBr) spectra were recorded on a Perkin-Elmer 221 infrared spectrophotometer and 90 MHz PMR ($CDCl_3$) on a varian instrument using TMS as internal standard.

3-[*p*-(*N-Methyl-N-phenyl-carbamoyl*)]*phenylsydnone* (**Ia**)

(i) *p*-Amino-N-methyl-N-phenybenzamide was reacted with ethylbromoacetate in equimolar quantities according to the literature method[4] and the separated ester crystallised from ethanol to give Ia (80%), m.p. 84° (Found: C, 69.4; H, 6.6; N, 8.8. $C_{18}H_{20}N_2O_3$ requires C, 69.2; H, 6.4; N, 9.0%).

(ii) Alkaline hydrolysis of the above ester yielded the corresponding glycine which crystallised from ethanol (53%), m.p. 100° (Found: C, 67.4; H, 5.7; N, 9.8. $C_{19}H_{16}N_2O_3$ requires C, 67.6; H, 5.6; N, 10.0%).

(iii) Nitrosation of the above glycine was carried out and the resulting nitroso compound crystallised

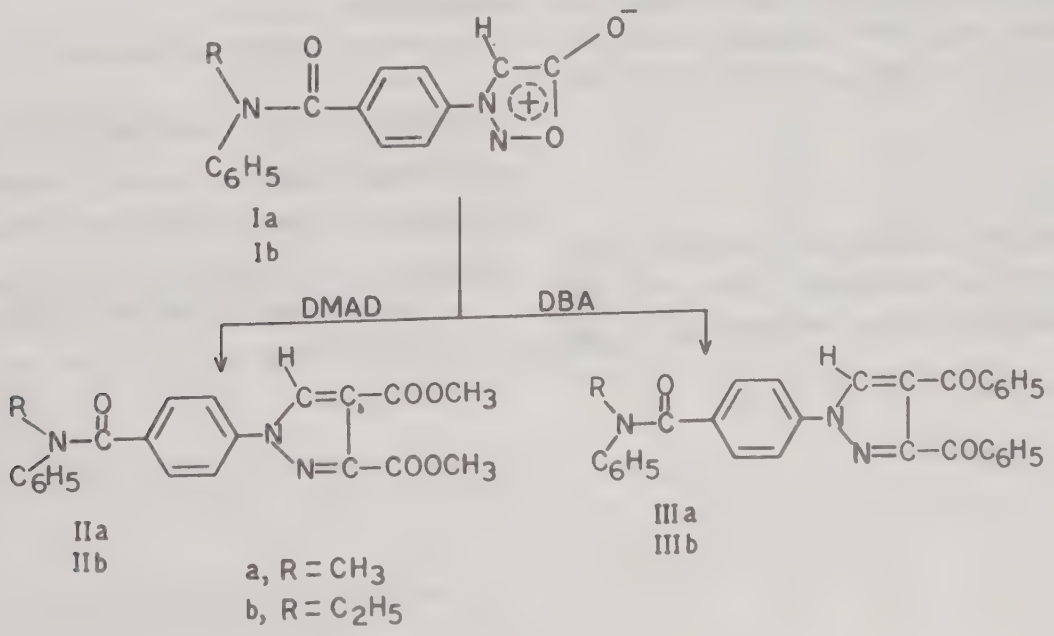

Table 1 – Antibacterial Activity Data of Compounds I-III at Concentrations: (A) 100 μg/0.1 ml, (B) 50 μg/0.1 ml, and (C) 25 μg/0.1 ml.

(Solvent: DMF)

Compd	*Staphylococcus aureus*			*Pseudomonas pyocynea*			*Proteus vulgaris*			*E. coli*		
	A	B	C	A	B	C	A	B	C	A	B	C
Ia	29±	27±	26±	22±	19±	16±	29±	19±	16±	21±	17±	15±
Ib	28+	23+	14+	24±	22+	17+	31+	28±	18+	22+	18+	14+
IIa	28±	23	17±	25±	22±	18±	32±	26±	18±	22±	19±	16±
IIb	23±	19±	18±	23±	21±	20±	28±	23±	21±	19±	18±	16+
IIIa	41+	36+	34+	31±	29±	27±	36+	35 ±	34+	30+	29+	28+
IIIb	32+	28+	16+	28±	23±	17±	42±	36±	28±	19+	17+	12+
DMF	a	a	a	a	a	a	13+	a	a	12′	a	a
Phenol	17+	16+	16+	a	a	a	19+	19+	18+	14+	13+	a
Sulphanilamide	20+	18+	16+	18+	17+	16+	20+	19+	18+	14+	a	a

\+ Indicates complete inhibition.
± Indicates partial inhibition.
a Indicates no inhibition.

from ethanol (46%), m.p. 150° (Found: C, 61.4; H, 4.6; N, 13.2. $C_{16}H_{15}N_3O_4$ requires C, 61.3; H, 4.8; N, 13.4%).

(iv) The nitroso compound was cyclised with acetic anhydride on a boiling water-bath for 4 hr to give the sydnone (Ia) which crystallised from ethanol (57%), m.p. 156° (Found: C, 65.2; H, 4.6; N, 14.1. $C_{16}H_{13}N_3O_3$ requires C, 65.1; H, 4.4; N, 14.2%).

In a similar procedure the N-ethyl analogue (Ib) was prepared:

(i) The ester crystallised from ethanol (82%), m.p. 104° (Found: C, 69.6; H, 6.8; N, 8.8. $C_{19}H_{22}N_2O_3$ requires C, 69.6; H, 6.7; N, 8.6%).

(ii) The glycine crystallised from ethanol (53%), m.p. 155° (Found: C, 68.7; H, 6.4; N, 9.3. $C_{17}H_{18}N_2O_3$ requires C, 68.5; H, 6.0; N, 9.4%).

(iii) The nitroso compound crystallised from ethanol (47%), m.p. 130° (Found: C, 62.6; H, 5.2; N, 12.8. $C_{17}H_{17}N_3O_4$ requires C, 62.4; H, 5.2; N, 12.8%).

(iv) The sydnone (Ib) crystallised from ethanol as yellow needles yield 64% m.p. 131° (Found: C, 66.4; H, 4.8; N, 13.6. $C_{17}H_{15}N_3O_3$ requires C, 60.0; H, 4.9; N, 13.6%).

Pyrazoles (II,III)

These were obtained by reacting the sydnones (Ia,b) with DMAD and DBA in refluxing xylene. All the pyrazoles were crystallised from benzene-pet. ether (60-80°) and their characterization data are given in Table 2.

Table 2 – Characterization Data of Pyrazoles (II,III)

Compd	Yield (%)	m.p. °C	Mol. formula	Found (%) C	Found (%) H	Calc. C	Calc. H
IIa	52	138	$C_{21}H_{19}N_3O_5$	64.3	4.7	(64.1	4.8)
IIb	60	144	$C_{22}H_{21}N_3O_5$	64.9	5.4	(64.9	5.2)
IIIa	50	151	$C_{31}H_{23}N_3O_3$	76.6	4.8	(76.7	4.8)
IIIb	53	102	$C_{32}H_{25}N_3O_3$	76.8	5.0	(77.0	5.0)

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Nuclear Magnetic Resonance: Part V†—Variable Temperature ^{13}C NMR Spectral Studies on Indole-1-carboxaldehydes

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Carbon-13 NMR spectra of 3-ethylindole-1-carboxaldehyde (**1**) and 3-phenylindole-1-carboxaldehyde (**2**) have been recorded at variable temperatures and the assignments of the chemical shifts of various carbons made. Both are found to exist in *E*- and *Z*-conformations at ambinet temperature. The signals for C-7 of the *Z*-rotamers of **1** and **2** appear downfield ($\Delta\delta = 8.41$ ppm and 7.96 ppm, respectively) owing to the electric field effect of the carbonyl oxygen in comparison to those for the same carbons of their *E*-rotamers. As C-2 of only the *Z*-rotamers of **1** and **2** are located at γ-position and anti-periplanar to the carbonyl oxygen, their signals appear upfield ($\Delta\delta = 7.04$ ppm and 9.34 ppm, respectively) as compared to those for the corresponding carbons of their *E*-rotamers. The spectrum of the weighted average of the two rotamers of each of **1** and **2** is observed at elevated temperature (100°C).

We have recently reported for the first time the ^{13}C NMR spectral studies on 2,3-disubstituted indole-1-carboxaldehydes at ambient temperature[1]. Although variable temperature ^{13}C NMR spectral studies on 9-acetylcarbazole[2,3] and other 9-acyl derivatives of carbazole[3] yielded interesting results, no such study on indole-1-carboxaldehydes seems to have appeared in the literature so far. We, therefore, studied the variable temperature ^{13}C NMR spectral features of **1** and **2** which were synthesized for other purposes[4-8].

The ^{13}C NMR chemical shifts of **1** and **2** at variable temperatures are given in Table 1. The assignments, specially of C-2 and C-7, were made on the grounds described earlier[1] and also by correlation with the ^{13}C NMR spectral data of 2,3-di-substituted-indole-1-carboxaldehydes[1], 1-acetylindole[2] and substituted 1-acetylindoles[9].

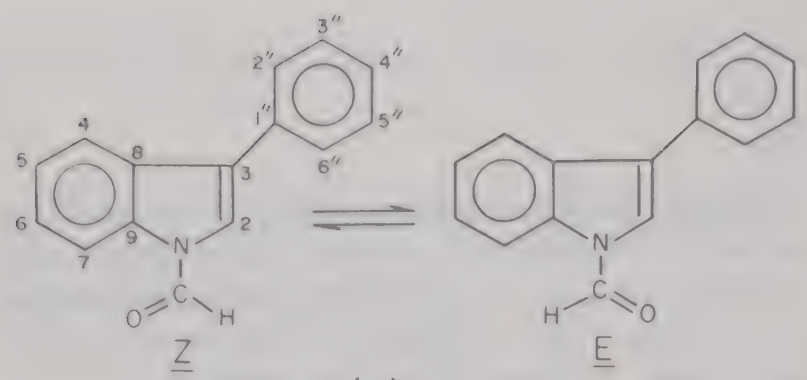
Both **1** and **2** in their ^{13}C NMR spectra at ambient temperature, showed two sets of resonances for each of the C-2, C-3, C-7 and the carbonyl carbon (Table 1). The methyl protons of **1** appeared as a double triplet in its ^{1}H NMR spectrum at -5°C. Its methylene and methyl carbons resonated as a double triplet and a triple quartet, respectively in its 400 MHz SFORD ^{13}C NMR spectrum at the ambient temperature. These observations indicated the existence of **1** and **2** in *E*- and *Z*-conformations around ambient temperature, as observed earlier by ^{1}H NMR spectral analysis[7]. At 100°C, the respective carbons of both the rotamers of each compound became magnetically equivalent, because of the increased rate of rotation about the N—CHO bond and only the spectrum of the weighted average of *E*- and *Z*-rotamers was obtained in each case.

Table 1—Carbon-13 NMR Chemical Shifts of 3-Ethylindole-1-carboxaldehyde (**1**) and 3-Phenylindole-1-carboxaldehyde (**2**) in DMSO-d_6 at Variable Temperatures and Their Assignments*

Compd.	Temperature	Conformer	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	CHO
1	Ambient[a]	*Z*	115.23	124.90	119.20	123.72	124.51	119.20	130.85	134.45	160.72
		E	124.51	122.33	119.20	123.72	124.51	111.64	130.85	134.45	158.01
	Ambient[b,c]	*Z*	115.28	124.34	119.11	123.70	124.43	119.11	131.00	134.36	160.67
		E	122.32	121.31	119.11	123.70	124.43	110.70	131.00	134.36	157.36
	100°C[d]	Coalesced form	118.97	124.83	120.28	123.42	124.27	113.70	130.62	134.34	159.14
2	Ambient[b,e]	*Z*	115.52	126.62	119.95	124.37	124.86	119.95	128.72	134.73	161.12
		E	124.86	123.17	119.95	124.37	124.86	111.99	128.72	134.73	160.76
	100°C[f]	Coalesced form	119.71	123.01	121.82	124.10	124.59	113.72	129.99	134.65	159.62

*The numbering of the carbons corresponds to that given in structure **2**.
[a]3-CH_2-CH_3 17.56, 13.02.
[b]Spectra were recorded on a Bruker WM-400 (400 MHz) NMR spectrometer.
[c]3-CH_2-CH_3 17.47, 12.97.
[d]3-CH_2-CH_3 17.54, 12.47.
[e]C-1″ 132.83, C-2″ + C-6″ 127.37, C-3″ + C-5″ 128.90, C-4″ 127.37.
[f]C-1″ 132.59, C-2″ + C-6″ 127.11, C-3″ + C-5″ 128.61, C-4″ 127.11.

†Part IV: Biswas K M, Dhara R N, Mallik H & Roy S, *Indian J Chem*, **24B** (1985) 654.



Z ⇌ E

(2)

By ^{1}H NMR spectral analysis, the *Z*-conformer of **1** was found to be more populated than its *E*-conformer[7]. Therefore, assignments for the carbonyl carbon, C-2, C-3 and C-7 of the two rotamers of **1** were made on the basis of the relative intensities of the two signals for each of these carbons[10], on the grounds mentioned earlier[1] and also by correlation with the spectral data of 1-acetyl-3-ethylindole[9], 1-acetyl-3-methylindole[9], 1-acetylindole[2] and 2,3-disubstituted indole-1-carboxaldehydes[1]. Since the exact populations of the two rotamers of **2** could not be ascertained by ^{1}H NMR spectrum at 23°C[7], the CMR assignments for C-2, C-3, C-7 and the carbonyl carbon of the two rotamers of **2** were made by correlation with the spectral data of **1**, 1-acetylindole[2], 3-phenylindole[11], 1-acetyl-3-phenylindole[9] and 1-acetyl-3-methylindole[9], and also on the grounds recorded elsewhere[1].

The signals due to C-2 of the *Z*-rotamers of **1** and **2** appeared upfield ($\Delta\delta = 7.04$ ppm and 9.34 ppm, respectively) in comparison to those for the same carbons of their *E*-rotamers, probably because C-2 atoms of only the *Z*-conformers are located at γ-position and anti-periplanar to the carbonyl oxygen[12].

The signals due to C-7 of the *Z*-rotamers of **1** and **2** appeared downfield ($\Delta\delta = 8.41$ ppm and 7.96 ppm, respectively) as compared to those for the corresponding carbons of their *E*-conformers, because C-7 atoms in the *Z*-rotamers are close to the carbonyl oxygen and experience its electric field effect, whereas the same carbons in the *E*-conformers are away from the carbonyl oxygen and do not experience its electric field effect, although both are located at δ-position with respect to the carbonyl oxygen[1,13,14]. The same effect also caused downfield shift ($\Delta\delta = 3.31$ ppm and 0.36 ppm, respectively) in the signals due to carbonyl carbons of the *Z*-conformers of **1** and **2** compared to the signals for the corresponding carbons of their *E*-rotamers[13,14].

The signals due to C-3 of the *Z*-conformers of **1** and **2** appeared downfield ($\Delta\delta = 3.03$ ppm and 3.45 ppm, respectively) as compared to those for the corresponding carbons of their *E*-rotamers, but the reason is not clear to us.

Gilchrist *et al.*[11] have reported that the *para*-carbons of phenylindoles resonate at a lower-field than the *ortho*-carbons. However, in the present study we have found that these carbons of **2** resonate at the same position[cf. 1,8,9] (Table 1).

Unless otherwise stated, all the ^{13}C NMR spectra were recorded on a Varian CFT-20 NMR spectrometer at 80 MHz at ambient temperature (24°C) and at 100°C in DMSO-d_6 using the solvent as internal lock and internal standard. Other experimental conditions were similar to those reported earlier[1]. The compounds were subjected to PND and SFORD to establish the carbon shifts and degree of protonation. The chemical shifts reported are in δ(ppm) downfield from TMS; $\delta_{TMS} = \delta_{DMSO-d_6} + 39.6$ ppm. The syntheses of **1** and **2** have been recorded earlier[4,5].

The authors are grateful to Prof. (Mrs) A Chatterjee for her interest in the work and RSIC, CDRI, Lucknow for recording the 400 MHz ^{13}C NMR spectra. One of them (K M B) is grateful to Prof. H C Brown and Mr J Burnes, Purdue University, USA for laboratory facilities and assistance in recording the ^{13}C NMR spectra at 100°C, respectively, to UNESCO, Paris for a fellowship and Purdue University, USA for a Visiting Assistant Professorship. Three of them (D G, H M and S R) thank the UGC, New Delhi for financial assistance.

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Configurational Assignment of the Diels-Alder Adducts of Cyclopentadiene & 9,10-Dihydro-9,10-ethenoanthracene-11,12-dicarboxylic Anhydride by PMR Spectroscopy

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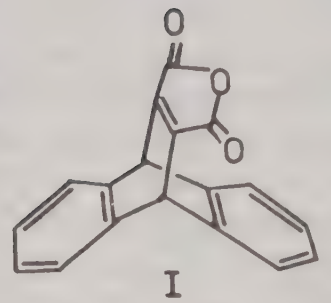
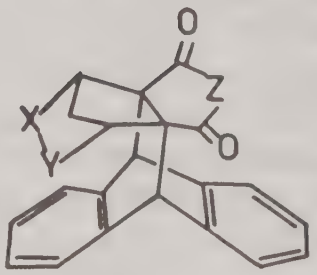
9,10-Dihydro-9,10-ethenoanthracene-11,12-dicarboxylic anhydride (I) reacts with cyclopentadiene to give a mixture of two isomeric adducts: *endo* (25%) and *exo* (60%), the configurations of which have been established by PMR resonances of 7′-methylene hydrogens. The PMR data of their dibromo and N-(N′,N′-diacetylamino)imide derivatives further support the assigned configurations. The *endo*-adduct is found to be more reactive towards hydrazine hydrate than the *exo*-isomer. 6,6-Dimethylfulvene on reaction with I forms the adduct X which has been characterized as the *endo*-isomer by its PMR spectral data.



I



II & III X—Y = CH=CH, Z = O

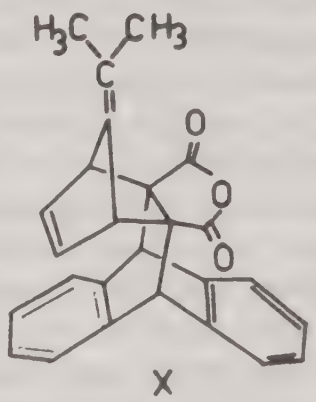
IV & V X—Y = CH_2—CH_2, Z = N—NH_2

VI & VII X—Y = CH_2—CH_2, Z = N—$N(COCH_3)_2$

VIII & IX X—Y = CHBr—CHBr, Z = O

The reaction of cyclopentadiene with 9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylic anhydride (I)[1] is expected to give two isomeric adducts (*endo* and *exo*), but the formation of only one isomer (II), having *exo*-orientation of the olefinic bond of the norbornene ring, was reported[2]. We report herein the formation of both the isomers and the assignment of their configurations based on a comparative study of their PMR spectra and also of their dibromo and N-aminoimide derivatives. 6,6-Dimethylfulvene on reaction with anhydride (I) produced an adduct (X) which was characterized as *endo*-isomer by its PMR data.

The shielding parameter ($\Delta\delta \simeq 1$ ppm) of 7′-methylene protons which appeared as an *AB* quartet in the adduct (II) showed the anisotropic effect of the cage benzo-ring on one of the protons (H_B)[3] whereas the normal resonances for 5′- and 6′-protons suggested the *exo*-orientation for the olefinic bond of the norbornene ring (**1**). An *endo*-orientation (**2**) for the olefinic bond was proposed in adduct III based on the shielding parameter ($\Delta\delta \simeq 1$ ppm) of 5′- and 6′-protons which was further substantiated by the normal resonances of the 7′-methylene protons. This orientation (**2**) of the norbornene ring is assumed to be less favoured due to the non-bonded repulsion between the π-electron systems of the olefinic bond and the anthracene cage and it may be possible explanation for the lower yield of the adduct III.

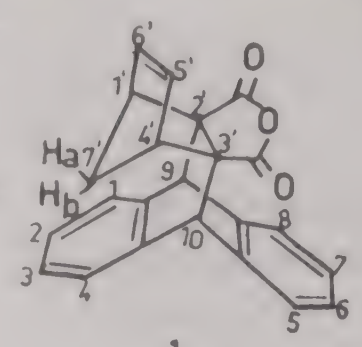


X

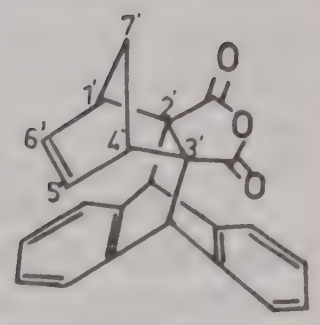
The adduct II on reaction with hydrazine hydrate in ethanolic medium failed to yield the N-aminoimide[4] derivative; however, on refluxing with a catalytic amount of animal charcoal, the N-aminoimide (IV; Table 1) derivative was obtained with the reduction of the olefinic bond[5]. The configurational structure **3** for IV was deduced from its PMR data[5]. On the other hand, the anhydride III readily reacted with hydrazine hydrate at room temperature and formed the N-

Table 1 – Melting Points and Elemental Analysis of the Compounds I-X

Compd	m.p. °C	Molecular formula	Found(%) (Calc.)	
			C	H
I	247	$C_{18}H_{10}O_3$	78.9 (78.8	3.5 3.7)
II	285	$C_{23}H_{16}O_3$	81.0 (81.2	4.8 4.7)
III	226	$C_{23}H_{16}O_3$	81.4 (81.2	4.7 4.7)
IV	302	$C_{23}H_{20}N_2O_2$	77.3 (77.5	5.5 5.7)
V	239	$C_{23}H_{20}N_2O_2$	77.4 (77.5	5.5 5.7)
VI	267	$C_{27}H_{24}N_2O_4$	73.5 (73.6	5.4 5.5)
VII	224	$C_{27}H_{24}N_2O_4$	73.8 (73.6	5.5 5.5)
VIII	268	$C_{23}H_{16}Br_2O_3$	55.5 (55.2	3.5 3.2)
IX	175	$C_{23}H_{16}Br_2O_3$	55.2 (55.2	3.3 3.2)
X	196	$C_{26}H_{20}O_3$	82.3 (82.1	5.1 5.3)



1



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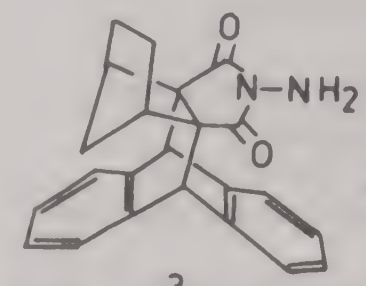

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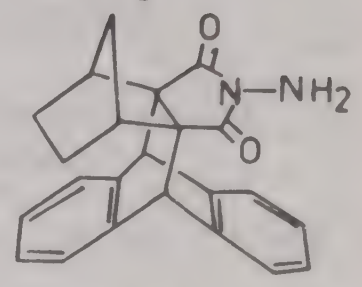

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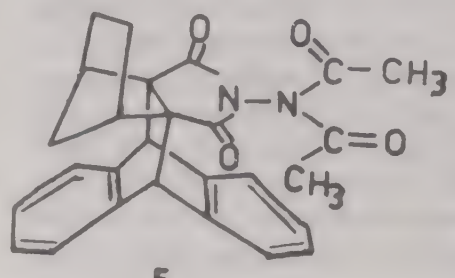

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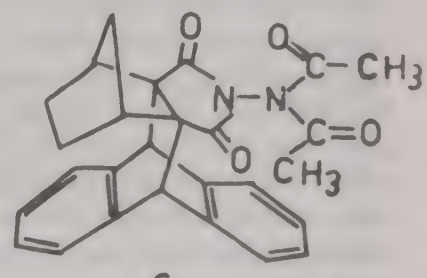

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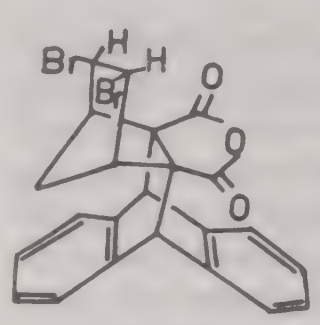
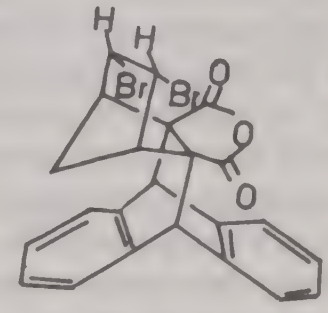
aminoimide derivative (V; **4**) (Table 1) with the reduction of the olefinic bond[6]. The facile reduction of the olefinic bond demonstrates the non-bonded repulsion between the two π-electron systems (cage and olefinic) in III and thus provides an additional evidence in support of the *endo*-orientation of the olefinic bond.

The N-(N′,N′-diacetylamino)imide derivatives provide additional evidence for the geometry of the molecule[4,7,8]. Compound VI showed two singlets each of 3H intensity for the N′-acetyl protons ($\Delta\delta = 1.72$ ppm) and a broad multiplet at δ 1.59-2.03 for 5′- and 6′-methylenic protons whereas compound VII displayed a broad multiplet for the 7′-methylene protons and two singlets due to N′-acetyl protons ($\Delta\delta = 1.66$ ppm). The nature of resonances due to acetyl protons shows restricted rotation and non-planar conformations about the N−N′ bond and the magnetic non-equivalence could be accounted for the shielding of *syn*-N′-acetyl by the cage benzo ring. However, the deshielding of the 5′- and 6′-methylenic protons ($\Delta\delta \simeq 0.5$ ppm) in VI shows that these protons are under the anisotropic effect of *anti*-N′-acetyl carbonyl[8], whereas the normal resonances for 7′-methylene protons in VII depict its least interaction with the *anti*-N′-acetyl carbonyl[9].

The dibromo derivative (VIII) showed an *AB* quartet (2H) ($\delta AB = 1.65$ ppm) due to 7′-methylene protons and a doublet (2H) at δ 4.20 for 5′- and 6′-CHBr methine protons. Appearance of the −CHBr methine protons as a doublet shows *cis*-addition of



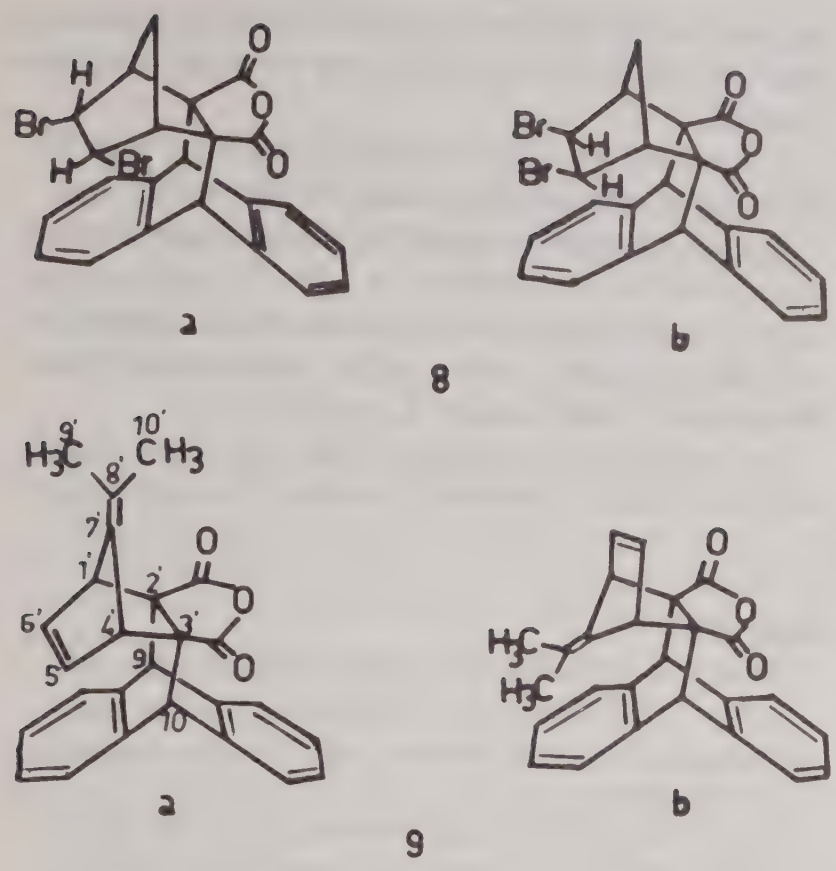
a



b

7

bromine atoms[10–12], which may take place either from the methylene bridge side (**7a**) or from the side of the succinic anhydride ring (**7b**). A large internal chemical shift due to 7′-methylene protons favours the *cis*-addition from the methylene bridge side[10] and the normal resonances for the methine protons support the *exo*-orientation of the olefinic bond. However, the dibromide IX exhibited an *AB* quartet (2H) ($\delta AB = 0.73$ ppm) due to 7′-methylene protons and a doublet (2H) at δ 3.19 for −CHBr methine protons. A *trans*-geometry (**8a**) could be expected for IX which would show magnetic non-equivalence of 5′- and 6′-methine protons[10]. Appearance of 5′- and 6′-methine protons as a doublet and the increased internal chemical shift of the methylene protons suggest *cis*-addition of bromine atoms from the methylene bridge side (**8b**). Further, the shielding parameter ($\Delta\delta \simeq 1$ ppm) of the



–CHBr methine protons suggests an *endo*-orientation for the olefinic bond in the adduct III.

The dienophile (I) may also undergo Diels-Alder reaction with .6,6-dimethylfulvene resulting in two configurational isomers, *endo* (**9a**) and **exo** (**9b**)[13,14]. In the present investigation only one isomeric adduct (X) was obtained, which showed a singlet (6H) at δ 1.45 for 9′- and 10′-methyl protons and a triplet (2H) at 5.25 for 5′- and 6′-olefinic protons along with the other proton resonances (Table 2). The shielding parameter ($\Delta\delta \simeq 1$ ppm) of the olefinic protons indicates an *endo*-orientation for the olefinic bond (**9a**) which was further supported by the signal due to 9′- and 10′-methyl protons appearing at normal position. Molecular model shows that the *exo*-orientation of the olefinic bond (**9b**) has a great steric interaction between methyl groups and the cage benzo ring and is less favoured.

PMR spectra were recorded in $CDCl_3$ on 90 MHz and 60 MHz spectrometers using TMS as internal standard and IR spectra in nujol mull on Perkin-Elmer 257 and 720 spectrophotometers. Carbon and hydrogen analysis were determined on a Colman carbon and hydrogen analyser. The required 9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylic anhydride (I) was obtained by heating 9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylic acid with acetic anhydride.

Bicyclo[2.2.1]*hept-5′-ene-2′,3′-exo/endo-*(9,10-*dihydro*-9,10-*anthraceno*)-2′,3′-*endo/exo-dicarboxylic anhydride* (*II/III*)

Finely powdered anhydride I (2 g) was mixed with freshly distilled cyclopentadiene (60 ml) and the

Table 2 – PMR Spectral Data of the Compounds II-X in $CDCl_3$ (Chemical shifts in δ, ppm)

Compd	(1′+4′) Protons	(5′+6′) Protons	7′-Protons	(9+10) Protons	Ar–*H*	N′-Acetyl/N′–H Protons	
II	2.96(*t*,2H) (J=1.5Hz)	6.34(*t*,2H) (J=1.5Hz)	0.65(AB_q,2H) (A=1.16, B=0.15) (J=12Hz)	4.61(*s*,2H)	6.97-7.35(*m*,8H)	—	—
III	3.10(*t*,2H) (J=1.5Hz)	5.08(*t*,2H) (J=1.5Hz)	1.48(AB_q,2H) (A=1.58, B=1.40) (J=9Hz)	4.40(*s*,2H)	6.93-7.38(*m*,8H)	—	—
IV	2.50(*bs*,2H)	1.08-1.53 (*bm*,4H)	0.15(*d*,1H)(J=10Hz) 1.08-1.53(*bm*,1H)	4.58(*s*,2H)	6.90-7.30(*m*,8H)	3.55(*s*,1H)*	3.55(*s*,1H)*
V	2.66(*bs*,2H)	0.93-1.66 (*bm*,4H)	0.93-1.66(*bm*,2H)	4.53(*s*,2H)	6.76-7.36(*m*,8H)	3.49(*s*,1H)*	3.49(*s*,1H)*
VI	2.66(*bs*,2H)	1.59-2.03 (*bm*,4H)	0.57(AB_q,2H) (A=1.00, B=0.15) (J=9 Hz)	4.83(*s*,2H)	7.10-7.50(*m*,8H)	2.66(*s*,3H)	0.94(*s*,3H)
VII	2.68(*bs*,2H)	0.85-1.65 (*bm*,4H)	0.85-1.65(*bm*,2H)	4.53(*s*,2H)	6.70-7.33(*m*,8H)	2.36(*s*,3H)	0.70(*s*,3H)
VIII	2.83(*bs*,2H)	4.20(*d*,2H)	1.02(AB_q,2H) (A=1.85, B=0.20) (J=12Hz)	4.75(*s*,2H)	7.05-7.33(*m*,8H)	—	—
IX†	3.53(*bs*,2H)	3.19(*d*,2H)	2.29(AB_q,2H) (A=2.66, B=1.93) (J=10Hz)	4.50(*s*,2H)	7.26-7.63(*m*,8H)	—	—
X	3.65(*t*,2H) (J=1.5Hz)	5.25(*t*,2H) (J=1.5Hz)	1.45(*s*,6H)	4.50(*s*,2H)	7.05-7.35(*m*,8H)	—	—

* D_2O exchangeable.
† The spectrum was recorded in DMSO-d_6.

mixture refluxed with gentle shaking for 45 min when a clear solution resulted in. It was cooled and the solid, thus obtained, was filtered and recrystallized from benzene to give II (yield 60%). After removal of the excess of cyclopentadiene under reduced pressure from the mother liquor, another solid product was obtained which on recrystallization from benzene afforded III (yield 25%). The characterization data of II and III are given in Table 1.

Preparation of the compounds IV, V, VI and VII (*Table* 1)

Compound IV was obtained by the method of Furst *et al.*[5] by refluxing II with hydrazine hydrate and animal charcoal in ethanol for 3 hr and recrystallized from ethanol.

Compound V was obtained by stirring III with an equimolar amount of hydrazine hydrate in ethanol at room temperature for 3 hr and recrystallized from ethanol.

Compounds VI and VII were obtained by heating the corresponding N-aminoimides (IV and V) with an excess of acetic anhydride for 4 hr. The solvent was removed under reduced pressure and the products thus obtained were washed, filtered, dried and re-crystallized from ethanol.

Preparation of the dibromides (*VIII and IX*)

These compounds were obtained by the method of Bartlett and Schneider[15]. The adduct II (1 g) was dissolved in dry chloroform (15 ml) and treated with bromine in chloroform (0.5 g/15 ml). Illumination initiated a vigorous reaction and a solid separated out after 1 hr. The product VIII was recrystallized from benzene.

Compound IX was obtained in a similar way III.

Diels-Alder adduct (*X*) *of I and* 6,6-*dimethylfulvene*

Equimolar proportions of I and 6,6-dimethylfulvene were heated in dry benzene for 2 hr. The solution was cooled, the solvent removed under reduced pressure, and the resultant white solid recrystallized from benzene-pet. ether to give X, yield 60%.

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A New Limonoid Glycoside from the Stem Bark of *Melia azedarach* Linn.

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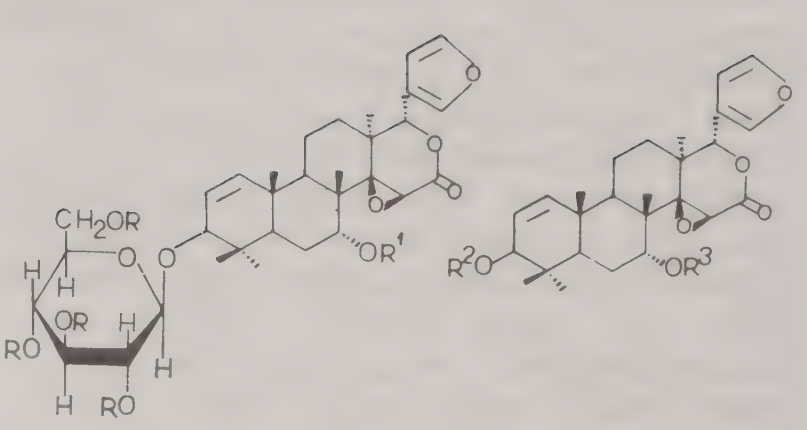
Chemical and spectral evidences are presented for characterizing a new limonoid glycoside as 7α-acetoxy-14β,15β-epoxy-gedunan-1-ene-3-O-β-D-glucopyranoside (I) isolated from the stem bark of *Melia azedarach* Linn.

Previous study on the plant of *Melia azedarach* has disclosed the presence of a large number of limonoids[1]. We report herein the isolation and structure elucidation of a new limonoid glycoside, 7α-acetoxy-14β,15β-epoxy-gedunan-1-ene-3-O-β-D-glucopyranoside (I) on the basis of chemical and spectral data.

Compound-I, m.p. 110-12°, $C_{34}H_{46}O_{12}$, $[\alpha]_D^{25} - 85^c$ ($CHCl_3$), responded positively to the reactions characteristic of glycosides[2]. It showed a strong UV (EtOH) band at 285 nm (log ε 1.8) showing the presence of a furan group[3-6]. The same conclusion was also drawn from the IR(KBr) spectrum of I (2940, 1510 and 875 cm^{-1} for β-substituted furan). It formed a tetramethyl ether ($Me_2SO_4 - K_2CO_3$), m.p. 130-32° (d) and a pentaacetate (II) ($Ac_2O - C_5H_5N$), m.p. 110-12°. The PMR of II was closely related to gedunin, khivorin and its derivatives[7]. Acid hydrolysis of I afforded the genin III and D-glucose (co-PC and osazone). The genin (III) formed a diacetate (IV) and on Sarrett Oxidation[8,9] ($CrO_3 - C_5H_5N$) produced gedunin[5]. Deacetylation of III yielded the diol (V) which on Sarrett oxidation afforded deacetoxy-7-oxogedunin[10]. Based on above evidences the structure of the genin(III) was established as 7α-acetoxy-3β-hydroxy-14β,15β-epoxy-gedunan-1-ene, the mass spectrum of which was also in good agreement with the proposed structure.

The periodate oxidation[11] of I in 90% ethanol at room temperature consumed 2 moles of periodate with the liberation of 1 mole of formic acid per mole of I after 80 hr indicating the presence of D-glucose in pyranose form. The hydrolysis of I with almond emulsin liberated D-glucose (co-PC) and the genin III (m.p., m.m.p. and co-TLC) indicating the presence of β-glycosidic linkage. Thus, the new limonoid glycoside was assigned the structure 7α-acetoxy-14β,15β-epoxygedunan-1-ene-3-O-β-D-glucopyranoside (I).



(I) : R = H ; R^1 = Ac
(II) : R = R^1 = Ac
(III) : R^2 = H ; R^3 = Ac
(IV) : R^2 = R^3 = Ac
(V) : R^2 = R^3 = H

Isolation of limonoid glycoside (I)

Air-dried and powdered stem bark of *Melia azedarach* (5 kg), procured from the United Chemicals and Allied Products, Calcutta, was exhaustively extracted with ethanol under reflux on a water-bath for 25 days. The ethanol extract (30 litres) was concentrated under reduced pressure to get a solid mass (10 g) which was extracted successively with refluxing pet. ether (b.p. 60-80°) and benzene. The benzene extract (1 liter) was concentrated to give a dirty white mass (3.2 g) which was chromatographed over silica gel using chloroform as eluent. The eluate was concentrated and the compound repeatedly crystallized from $CHCl_3 - C_6H_6$ to get I as a TLC-pure, colourless crystalline substance, yield 2.9 g, m.p. 110-12°; $[\alpha]_D^{25} - 85°$ ($CHCl_3$); IR(KBr): 3450 (OH), 1720 (acetate), 1740 (lactone ring), 825 (glycoside) and 2940, 1510 and 875 cm^{-1} (β-substituted furan) (Found: C, 63.1; H, 7.1. $C_{34}H_{46}O_{12}$ requires C, 63.2; H, 7.1%). It formed a tetramethyl ether (100 mg I + 6 ml Me_2SO_4 + 2 g K_2CO_3, yield 65 mg), m.p. 130-32° (Found: C, 64.9; H, 7.6. $C_{38}H_{54}O_{12}$ requires C, 65.0; H, 7.7%) and a pentaacetate (II) (100 mg I + 5 ml Ac_2O + 5 ml C_5H_5N, yield 85 mg), m.p. 110-12°; IR(KBr): 1740 (lactone), 1720 cm^{-1} (acetate); PMR($CDCl_3$, TMS, 90 MHz) δ 7.39 (*m*, 1H, α-H of furan), 7.20 (*m*, 1H, α-H of furan), 6.90 (*dd*, *J* = 6 and 10 Hz, 1H, H-2), 6.40 (*m*, 1H, α-H of furan), 6.15 (*d*, *J* = 10 Hz, 1H, H-1), 5.65 (*s*, 1H, H-17), 4.50 (*t*, *J* = 4 Hz, 1H, H-7 axial and α-configuration)[9], 4.30 (*d*, *J* = 6 Hz, 1H, H-1'), 3.90 (*d*, *J* = 6 Hz, 1H, H-3), 3.80 (*s*, 1H, H-15), 3.50-3.70 (*m*, sugar protons), 2.15, 2.10, 2.08, 2.05, 2.00 (each *s*, 5 × $OCOCH_3$), 1.20-1.90 (polymethylene CH_2 and CH), 1.18, 1.15, 1.10, 1.05, 0.90 (each *s*, 5 × CH_3) (Found: C, 61.8; H, 6.6. $C_{42}H_{54}O_{16}$ requires C, 61.9; H, 6.6%).

Acid hydrolysis of I

A solution of I (2.2 g) in ethanol (40 ml) and 7% H_2SO_4 (50 ml) was refluxed for 5 hr on a water-bath, poured into ice-cooled water (150 ml) and kept at room temperature for 24 hr. The precipitated genin (III) was filtered and the filtrate neutralized ($BaCO_3$) and was found to contain D-glucose (co-PC and osazone).

The genin (III) was purified by column chromatography over neutral Al_2O_3 using benzene as eluent. Attempted crystallization from benzene-pet. ether furnished the TLC-pure colourless needles of III, yield 1.85 g, m.p. 82-84°; UV(EtOH): 285 nm (furan): IR(KBr): 3440 (OH), 1740 (lactone), 1720 (acetate) and 2940, 1510 and 875 cm^{-1} (furan); PMR($CDCl_3$, TMS, 90 MHz): δ 7.40, 7.20, 6.90, 6.40, 6.15, 5.65, 4.50, 3.90, 3.80, 3.20 (*s*, OH, exchangeable with D_2O), 2.02 (*s*, 3H, $\times OCOCH_3$), 1.20-1.90, 1.18, 1.15, 1.10, 1.00, 0.90; MS: *m/z* 484 (M^+), 469, 466, 425, 417, 416, 403, 291 and 221 (Found: C, 69.4; H, 7.4. $C_{28}H_{36}O_7$ requires C, 69.4; H, 7.4%). The genin formed a diacetate (IV) (100 mg III + 5 ml Ac_2O + 5 ml C_5H_5N, yield 80 mg), m.p. 166-62°; IR(KBr) 1725 cm^{-1} (acetate); PMR($CDCl_3$, TMS, 90 MHz): δ 7.60, 7.20, 6.90, 6.40, 6.15, 5.60, 5.10 (*d*, $J=6$ Hz, H-3), 4.50, 3.80, 2.10 (*s*, 3H, $OCOCH_3$), 2.00 (*s*, 3H, $OCOCH_3$), 1.20-1.90, 1.18, 1.15, 1.10, 1.05, 0.90 (Found: C, 63.4; H, 7.2. $C_{30}H_{30}O_8$ requires C, 68.4; H, 7.2%).

Sarrett oxidation of III

Compound III (600 mg) in C_5H_5N (10 ml) was added with stirring to CrO_3 (600 mg, dried *in vacuo* over P_2O_5) and C_5H_5N (25 ml). The mixture was worked up as usual[1] to get the product which crystallized from benzene-pet. ether as colourless prisms (yield 310 mg) and was found to be identical with gedunin[5] in physical data {m.p. 216-17° (lit. 218°); $[\alpha]_D^{25}$ −40° ($CHCl_3$) (lit. −44°)}, spectral data and elemental analysis (Found: C, 69.5; H, 7.00. Calc. for $C_{28}H_{34}O_7$: C, 69.5; H, 7.1%).

Deacetylation of III

The genin III (200 mg) in MeOH (10 ml) was refluxed with 2*N* NaOH (10 ml) for 30 min. The solution was acidified (HCl) to get the diol (V) which crystallized from $C_6H_6-CHCl_3$ as plates, yield 180 mg, m.p. 144-46°; IR(KBr): 3450 (OH), 1740 (lactone), 2930, 1510, 875; PMR($CDCl_3$, TMS, 90 MHz): δ 7.40, 7.20, 6.90, 6.40, 6.15, 5.60, 3.90, 3.85, 3.35 (*t*, $J=6$ Hz, H-7), 3.25 (*s*, 1H, OH), 3.20 (*s*, 1H, OH), 1.20-1.90, 1.18, 1.15, 1.10, 1.00, 0.90 (Found: C, 70.5; H, 7.6. $C_{26}H_{34}O_6$ requires C, 70.6; H, 7.7%).

Sarrett Oxidation of V

The diol (V; 100 mg) on Sarrett oxidation as usual[1] gave deacetoxy-7-oxogedunin[10] (yield 55 mg) which was characterized by spectral data and elemental analysis (Found: C, 71.2; H, 6.8. Calc. for $C_{26}H_{30}O_6$: C, 71.2; H, 6.8%).

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BOOK REVIEWS

Asymmetric Catalysis, edited by B Bosnich (Martinus Nijhoff Publishers, Dordrech, Netherlands), 1986. pp. 160 + VIII. Price Dfl 115,00, US $ 45.50, £ 31.95.

Perhaps the most significant development in synthetic organic chemistry over the past decade has been the unprecendented growth in asymmetric synthesis using chiral auxiliaries, chiral catalysts and of course, chiral starting materials. The book under review deals with only one aspect mentioned above - namely asymmetric synthesis employing chiral catalysts and is the outcome of a workshop held on this topic in early 1984.

A brief introductory discussion on catalysis and asymmetric synthesis is given in Chapter 1. Chapter 2 is devoted to asymmetric carbon-hydrogen bond formation via catalytic hydrogenation, hydrogenation of ketones, double bond migration and hydrosilation. Carbon-carbon bond formation forms the subject of Chapter 3. The coverage, though brief, is informative and as many as nine different reactions (hydroformylation, hydrocarboxylation, hydrocyanation, allylic alkylation, Grignard cross-coupling, cyclopropanation, codimerization, cyclodimerization and Diels-Alder reaction) are presented. The celebrated Sharpless epoxidation and oxidation of sulfides constitute the oxidation reactions in Chapter 4. Heterogeneous and enzymatic catalysis are covered in Chapters 5 and 6 respectively. The economic importance of asymmetric catalysis is pointed out in Chapter 7 and the last chapter outlines the probable course of future trends in asymmetric catalysis.

In refreshing contrast to many publications arising from symposia or workshops, the book reads smoothly as the various participants instead of writing separate sections, have jointly presented summaries of the different topics which have been tightly edited. Thus, the text is brief and terse and the referencing selective and not comprehensive. At the same time clarity has not been sacrificed. Each section comprises a brief discussion on the development and scope of the particular reaction, its mechanism and finally pointers for future work and prospects.

A book of this kind, though not comprehensive, serves to highlight the growing importance of asymmetric catalysis in organic synthesis and is warmly recommended for careful study to all interested in asymmetric synthesis.

M. Nagarajan
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ANNOUNCEMENTS

IUPAC Recommendations on Nomenclature for Cyclic Organic Compounds with Contiguous Formal Double Bonds (the δ-Convention)

Substitutive (organic) nomenclature requires that the number of hydrogen atoms, if any, on each skeletal atom of a parent be known unambiguously. Trivial or semisystematic names are used to denote many rings and ring systems containing the maximum number of noncumulative double bonds. In order to use substitutive nomenclature and the same skeletal names when formal cumulative double bonds, actual or theoretical, are present in these rings and ring systems, a method for indicating the location of a cumulative double bond system is required. Techniques used up to now are either cumbersome or tend to use established techniques in ways other than for which they were designed. The λ-convention [*Pure & Appl Chem*, **56** (6) (1984) 769-778] for specifying nonstandard valency states of skeletal atoms, although useful, is not, by itself, sufficient for this purpose.

These rules provide a method for unambiguously denoting the presence of cumulative double bonds at a skeletal atom in a ring or ring system that otherwise has the maximum number of noncumulative double bonds. When combined with the λ-convention, where necessary, the number of hydrogen atoms available for substitution on such skeletal atoms is unambiguously known. The basic principles of this method were introduced briefly in Section D as revised for publication in the 1979 edition of the IUPAC Organic Nomenclature Rules (Pergamon Press).

The δ-convention is fully consistent with the fundamental principles of substitutive nomenclature which is based on formalized bonding in structural diagrams and is applicable to organic derivatives of inorganic chains and rings. It consists of a symbol, δ^c, where c is an arabic number representing the number of double bonds attached to the skeletal atom indicated by the preceding locant. A nonstandard valence state of the skeletal atom is given by the λ-convention, where necessary.

Comments on the report are welcome and should be sent before 31 May 1987 to the Secretary of Commission on Nomenclature of Organic Chemistry, Dr. W.H. Powell, Chemical Abstracts Service, POB 3012, 2540 Olentangy River Road, Columbus, Ohio 43210, USA.

Those desirous of having the full texts of these documents may write to the Executive Secretary, Indian National Science Academy, Bahadur Shah Zafar Marg, New Delhi 110 002.

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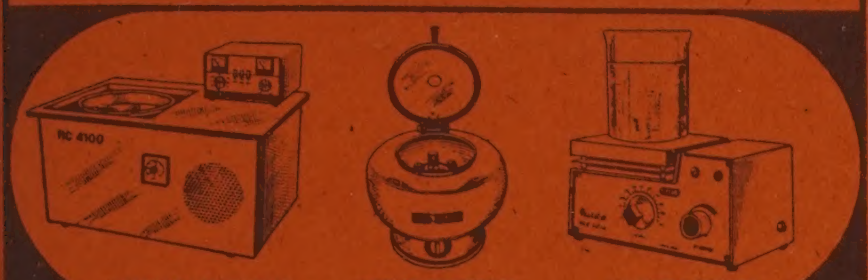

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